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Estimation of cancer risks and benefits associated with a potential increased consumption of fruits and vegetables

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ABSTRACT

The current paper provides an analysis of the potential number of cancer cases that might be prevented if half the U.S. population increased its fruit and vegetable consumption by one serving each per day. This number is contrasted with an upper-bound estimate of concomitant cancer cases that might be theoretically attributed to the intake of pesticide residues arising from the same additional fruit and vegetable consumption. The cancer prevention estimates were derived using a published meta-analysis of nutritional epidemiology studies. The cancer risks were estimated using U.S. Environmental Protection Agency (EPA) methods, cancer potency estimates from rodent bioassays, and pesticide residue sampling data from the U.S. Department of Agriculture (USDA). The resulting estimates are that approximately 20,000 cancer cases per year could be prevented by increasing fruit and vegetable consumption, while up to 10 cancer cases per year could be caused by the added pesticide consumption. These estimates have significant uncertainties (e.g., potential residual confounding in the fruit and vegetable epidemiologic studies and reliance on rodent bioassays for cancer risk). However, the overwhelming difference between benefit and risk estimates provides confidence that consumers should not be concerned about cancer risks from consuming conventionally-grown fruits and vegetables.

1. Introduction

Many consumers have significant concerns about the potential health effects of foods containing pesticide residues. In particular, surveys indicate that some consumers consider the presence of pesticides on food to be a serious cancer hazard (Gold et al., 2001). About 70% of respondents in a Spanish population considered avoiding pesticide-treated fruits and vegetables as a means to prevent cancer, and about 35% indicated that they acted on this belief (García et al., 1999). Another survey reported that organic food buyers estimated the risk of mortality from consuming conventionally-grown food to be at a level nearly as great as the annual lung cancer risk for a smoker of one pack or more of cigarettes per day (Hammitt, 1990). In 1988, controversial reports regarding the use of the growth regulator Alar (manufactured by Uniroyal) on apples resulted in "near hysteria" among parents, with sales of apples temporarily plummeting (American Dietetic Association, 2007). In contrast to the above consumer perceptions, many scientists have concluded that residues of pesticides on food are rarely of toxicological significance (e.g., Ames et al., 1987, 1990; Gold et al., 1992, 1997).

Concerns regarding pesticide residues and cancer need to be balanced with the potential health benefits of fruits and vegetables, including their potential cancer prevention benefits. The World Cancer Research Fund (WCRF) and American Institute of Cancer Research (AICR) recently published a meta-analysis of nutritional epidemiology studies investigating the potential for fruit and vegetable consumption to protect against cancer (WCRF/AICR, 2007). The report, "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective," was assembled by an expert panel and is widely cited in the literature. The report found "probable" evidence that eating fruits conveyed a protective effect for mouth, pharynx, larynx, esophageal, lung, and stomach cancer, and that eating vegetables protected against mouth, pharynx, larynx, esophageal, and stomach cancer. The report also found protective effects for the consumption of certain micronutrients associated with fruits and vegetables and different cancer types, including for folate (pancreas), carotenoids (mouth, pharynx, larynx, and lung), beta-carotene (esophagus), lycopene (prostate), and vitamin C (esophagus). Another meta-analysis of

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European epidemiological data by Soerjomataram et al. (2010) concluded that there were benefits for fruit and vegetable consumption for prevention of esophageal, pharynx, lung, and stomach cancer. In a large European study, Boffetta et al. (2010) found a 2–3% reduction in overall (not site-specific) cancer rates with fruit and vegetable consumption. The extent to which the lay public is aware of the potential health benefits of fruits and vegetable is unclear, illustrative of this about one-half of U.S. survey respondents did not identify fruit and vegetable consumption as a protective factor against cancer (National Cancer Institute, 1996).

A ratio of the potential positive health benefits from consuming fruits and vegetables compared to the potential risks associated with the ingestion of pesticide residues on fruits and vegetables can be estimated for cancer outcomes. With respect to predicting the increased risk for cancer as a consequence of the ingestion of pesticides associated with fruits and vegetables, the U.S. Environmental Protection Agency (EPA) has developed cancer risk factors for those pesticides that are considered animal carcinogens and there is a wealth of data on residue levels (collected annually by the U.S. Department of Agriculture; USDA, 2011) and food consumption (e.g., from population surveys by the U.S. Department of Agriculture; USDA, 1998) with which to estimate exposure. With respect to estimating the potential positive effects of diets high in fruits and vegetables, there is a wide array of literature on nutritional epidemiology that provides quantitative estimates of the potential cancer prevention benefits of fruit and vegetable consumption. Using information available in the above databases, for the current paper we calculated estimates of the reduced cases of cancer associated with eating more fruits and vegetables, and an upper-bound estimate (i.e., likely overestimated) of cancer cases due to an increased consumption of fruits and vegetables containing pesticide residues. We submit that this information can be useful for nutritionists and other health professionals who are queried about the potential effects of pesticide residues on fruits and vegetables. More broadly, it is suggested that the type of approach used in this paper provides a practical way to discuss and evaluate risk–benefit issues relating to the pros and cons of specific foods and their potential human health effects.

2. Materials and methods

2.1. Cancer prevention benefits of fruit and vegetable consumption

The 2007 WCRF/AICR report provides a meta-analysis of available epidemiologic studies for different cancer types and types of food, with separate estimates for case control and (likely more reliable) cohort studies. The meta-analysis results are presented as a relative risks, which represents the ratio of cancer incidence for populations with relatively higher consumption versus relatively lower consumption of fruits and vegetables.

The number of cancer cases prevented as a consequence of an increase in fruit and vegetable consumption can be estimated from the meta-analysis. The report provides relative risk estimates for different combinations of fruit and vegetable type and cancer type. Table 1 summarizes the relative risk estimates, including the 95th percentile confidence intervals. Only studies that associate benefits with fruit or vegetable consumption were considered, as opposed to studies that found associations for specific micronutrients. Considering the micronutrients would require assumptions about increased consumption for specific foods. For purposes of comparison with cancer cases associated with pesticide residues, the basis for the calculation is a hypothetical scenario in which one-half of the population increases their daily fruit and vegetable consumption by 80 g each (approximately one serving, depending on the commodity). An 80 g serving size definition is consistent with the Food and Agriculture Organization of the United Nations (FAO, 2012). For our calculations, half of the U.S. population was estimated to be 155 million (U.S. Census, 2011). The above scenario was chosen because the studies showing a benefit for eating fruits and vegetables generally compare populations with diets rich in fruits and vegetables to populations with relatively low intake of fruits and vegetables. Therefore, the scenario represents a situation in which the half of the population with the lowest intake increases daily consumption by one serving each of fruits and vegetables.

Table 1
Estimated cancer cases avoided from increasing fruit and vegetable consumption by one serving each.

Cancer type (grouped)	Food item	Study type	Relative risk (RR)[a]	Basis	Cancer type	Background cases per 100,000[b]		Cases potentially avoided per 80 g serving[c]
						Male	Female	
Mouth, pharynx, larynx	Non-starchy vegetables	Case-control	0.72 (0.63–0.82)	per 50 g	Oral cavity and Pharynx	15.7	6.2	8841
					Larynx	6.0	1.3	2947
Esophageal	Non-starchy vegetables	Case-control	0.87 (0.72–1.05)	per 50 g	Esophagus	7.8	1.9	1672
Esophageal	Raw vegetables	Case-control	0.69 (0.58–0.83)	per 50 g	Esophagus	7.8	1.9	4413
Stomach	Non-starchy vegetables	Cohort	0.98 (0.91–1.06)	per 100 g	Stomach	10.8	5.4	203
Stomach	Non-starchy vegetables	Case-control	0.70 (0.62–0.79)	per 100 g	Stomach	10.8	5.4	3545
Stomach	Green yellow vegetables	Cohort	0.63 (0.48–0.82)	per 100 g	Stomach	10.8	5.4	4560
Stomach	Green yellow vegetables	Case-control	0.59 (0.46–0.75)	per 100 g	Stomach	10.8	5.4	5180
Stomach	White or pale vegetables	Cohort	0.49 (0.24–1.01)	per 100 g	Stomach	10.8	5.4	6876
Stomach	White or pale vegetables	Case-control	0.57 (0.32–1.02)	per 100 g	Stomach	10.8	5.4	5502
Stomach	Raw vegetables	Cohort	0.80 (0.54–1.18)	per 100 g	Stomach	10.8	5.4	2232
Stomach	Raw vegetables	Case-control	0.50 (0.38–0.65)	per 100 g	Stomach	10.8	5.4	6696
Stomach	Allium vegetables	Cohort	0.55 (0.35–0.87)	per 100 g	Stomach	10.8	5.4	5832
Stomach	Allium vegetables	Case-control	0.59 (0.47–0.74)	per 100 g	Stomach	10.8	5.4	5180
Mouth, pharynx, larynx	Fruits	Cohort	0.82 (0.64–1.04)	per 100 g	Oral cavity and Pharynx	15.7	6.2	2686
					Larynx	6.0	1.3	895
Mouth, pharynx, larynx	Fruits	Case-control	0.72 (0.59–0.87)	per 100 g	Oral cavity and Pharynx	15.7	6.2	4421
					Larynx	6.0	1.3	1474
Mouth, pharynx, larynx	Citrus fruits	Case-control	0.76 (0.66–0.87)	per 50 g	Oral cavity and Pharynx	15.7	6.2	7406
					Larynx	6.0	1.3	2469
Esophageal	Fruits	Case-control	0.56 (0.42–0.74)	per 100 g	Esophagus	7.8	1.9	3393
Esophageal	Citrus fruits	Case-control	0.70 (0.56–0.88)	per 50 g	Esophagus	7.8	1.9	4245
Lung	Fruits	Cohort	0.94 (0.90–0.97)	per serving	Lung	75.2	52.3	6112
		Case-control	0.80 (0.68–0.94)	per serving	Lung	75.2	52.3	21958
Stomach	Fruits	Cohort	0.95 (0.89–1.02)	per 100 g	Stomach	10.8	5.4	515
		Case-control	0.67 (0.59–0.76)	per 100 g	Stomach	10.8	5.4	3969

[a] RR from 2007 WCRF/AICR meta-analysis report on cancer prevention.
[b] Background cancer rates from NIH SEER.
[c] Calculated from Eq. (2).

Table 2
Assignment of PDP data to surrogate commodities.

PDP commodity	Assigned surrogate commodities
Fruit	
Apple	Apple, crabapple
Apple juice	Apple juice, pear juice
Apple sauce	Apple sauce
Banana	Banana, Plantain
Blueberry	Blackberry, Blackberry juice, Blueberry, Blueberry juice, Boysenberry, Currant, Dewberry, Elderberry, Gooseberry, Huckleberry, Loganberry, Raspberry, Raspberry juice
Cantaloupe	Cantaloupe, Casaba, Honeydew
Cherry	Cherry
Cranberry	Cranberry
Grape	Grape, Grape juice, Wine and Sherry
Grapefruit	Grapefruit, Grapefruit juice, Pummelo
Nectarine	Nectarine
Orange	Citrus citron, Citrus hybrids, Kumquat, Lemon, Lime, Lime juice, Orange, Tangerine
Orange juice	Lemon juice, Lime juice, Orange juice, Tangerine juice
Peach	Apricot, Apricot juice, Peach, Peach juice
Pear	Loquat, Pear, Quince
Plum (dried)	Plum prune dried, Plum prune juice
Plum (fresh)	Plum, Plum prune fresh
Raisin	Raisin
Strawberry	Strawberry, Strawberry juice
Watermelon	Watermelon, Watermelon juice
Vegetables	
Asparagus	Asparagus
Beans	Black bean (seed), Broad bean (seed), Broad bean (succulent), Chickpea, Cowpea (seed), Cowpea (succulent), Great northern bean (seed), Guar (seed), Kidney bean (seed), Lima bean (seed), Lima bean (succulent), Mung bean (seed), Navy bean (seed), Pink bean (seed), Pinto bean (seed)
Broccoli	Broccoli, Chinese broccoli, Chinese mustard cabbage
Cauliflower	Cauliflower
Carrot	Burdock, Carrot, Carrot juice, Celeriac, Chicory roots, Garden beet, Ginseng, Horseradish, Parsley (turnip rooted), Parsnip, Radish, Rutabaga, Salsify roots, Sugar beet, Turnip roots
Celery	Cardoon, Celery, Celery juice, Celtuce, Fennel (Florence), Rhubarb, Swiss chard
Collard greens	Collard greens
Cucumber	Balsam pear, Chinese waxgourd, Cucumber
Eggplant	Eggplant
Green bean	Bean (snap succulent), Pea (edible podded succulent)
Green onion	Garlic, Green onion, Leek, Onion, Shallot
Kale	Broccoli raab, Brussels sprouts, Cabbage, Chinese bok choy cabbage, Chinese napa cabbage, Kale, Kohlrabi, Mustard greens, Rapegreens, Turnip greens
Lettuce	Head lettuce, Leaf lettuce, Radicchio
Peas	Lentil, Pea (dry), Pea (succulent), Pigeon pea (dry), Pigeon pea (succulent)
Peppers	Bell pepper, Nonbell pepper, Okra
Potato	Arrowroot, Cassava, Dasheen, Ginger, Jerusalem artichoke, Potato, Potato chips, Potato flour, Potato granules/flakes, Tanier, Turmeric, Yam, Yambean
Soybean	Soy milk, Soybean seed, Soybean flour, Soybean oil
Spinach	Amaranth, Arugula, Cress, Dandelion leaves, Endive, Garland chrysanthemum, Parsley, Spinach, Watercress
Summer squash	Chayote fruit, Pumpkin, Pumpkin seed, Summer squash
Sweet corn	Sweet corn
Sweet potato	Sweet potato
Tomato	Tomatillo, Tomato, Tomato juice, Tree Tomato
Winter squash	Winter squash

Table 1 summarizes each of the cancer type-consumption combinations reported for fruits and vegetables in the WCRF/AICR meta-analysis. In some cases, the results are presented for case control and cohort studies. Background cancer rates were assembled from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) (National Cancer Institute, 2012). Rates are available for males and females. The male and female rates were averaged and multiplied by the U.S. population to derive the background rate ($\overline{B}$) for each cancer type.

The portion of the population that has cancer due to its lack of fruit and vegetable consumption (and thus can be avoided by increasing their consumption) can be estimated using the population attributable risk (Levin, 1953):

$$PAR = \frac{Pe \times (RR - 1)}{(Pe \times (RR - 1) + 1)} \quad (1)$$

where: RR = relative risk (per serving size). Since the RR is less than 1 for the nutrition studies (the numerator is the group that consumed more fruits and vegetables), we need to use $1/RR$ in this formula. Pe = prevalence of group that needs to increase consumption (assumed to be ½).

The avoided cases are estimated by multiplying the PAR and the background rate and adjusting for the consumption rate that the RR is based onto a normalized serving size of 80 g:

$$\text{Avoided Cases} = PAR \times \overline{B} \times (80/SS) \quad (2)$$

where: SS = serving size that relative risk is based upon (either 50 or 100 g). Dividing 80 g by this number normalizes the result to a single serving size of 80 g.

Uncertainties associated with these estimates are reviewed in the discussion section.

2.2. Upper-bound estimate of cancer cases caused by pesticide residues

There are no epidemiologic studies that specifically address the cancer risk associated with pesticide residues. Therefore, standard risk assessment methods were utilized. The EPA has developed methodologies that can be applied to estimate cancer risk for the dietary consumption of pesticide residues on food (U.S. EPA, 2005). The general formula for estimating the lifetime risk associated with a given commodity–pesticide combination is as follows:

$$LR = \overline{C} \times \overline{R} \times Q_1^*/1000 \quad (3)$$

where: LR = lifetime cancer risk. $\overline{C}$ = average daily consumption of the commodity across the U.S. population (g/kg bw/day). $\overline{R}$ = average residue level of a pesticide on the commodity (mg/kg of commodity consumed). Q_1^* = cancer unit risk factor $(\text{mg/kg/day})^{-1}$.

The factor of 1000 (number of grams in a kilogram) adjusts $\overline{R}$ to the grams of commodity consumed.

Dietary consumption data from the Continuing Surveys of Food Intakes by Individuals (CSFII) conducted by the USDA in 1994–1996 and 1998 are used by the EPA to estimate dietary exposures to pesticide residues (USDA, 1998). The consumption data are programmed into the software model DEEM–FCID™ (Dietary Exposure Evaluation Model-Food Commodity Intake Database), which the EPA uses for die-

Table 3
Cancer unit risk values for pesticides.

Pesticide	Q_1^* (mg/kg/day)$^{-1}$	Source
Carbaryl	0.000875	U.S. EPA (2010)
Chlordane cis	0.35	U.S. EPA (2011a,b)
Carbendazim	0.00239	U.S. EPA (2010)
DCPA	0.00149	U.S. EPA (2010)
DDDo,p′	0.24	U.S. EPA (2011a,b)
DDDp,p′	0.24	U.S. EPA (2011a,b)
DDEp,p′	0.34	U.S. EPA (2011a,b)
DDTp,p′	0.34	U.S. EPA (2011a,b)
Dieldrin	16	U.S. EPA (2011a,b)
Diuron	0.0191	U.S. EPA (2010)
Fenbuconazole	0.00359	U.S. EPA (2010)
Fluometuron	0.018	U.S. EPA (2010)
Hexachlorobenzene (HCB)	1.6	U.S. EPA (2011a,b)
Imazalil	0.061	U.S. EPA (2010)
Permethrin cis	0.0096	U.S. EPA (2010)
Permethrin Total	0.0096	U.S. EPA (2010)
Permethrin trans	0.0096	U.S. EPA (2010)
Propargite	0.0033	U.S. EPA (2010)
Tetraconazole	0.023	U.S. EPA (2010)
Thiacloprid	0.0406	U.S. EPA (2010)
Trifluralin	0.0058	U.S. EPA (2010)

Note: Q_1^* values for cancer risk from U.S. EPA. The Q_1^* represents the probability of cancer occurring from an average lifetime exposure of 1 mg/kg/day. The source column provides the document that includes the Q_1^*.
Iprodione was listed as likely to be carcinogenic to humans in the EPA database; however, the most recent discussion of iprodione carcinogenicity states the dose–response is likely non-linear and should be regulated by a threshold approach (Federal Register, 2001).

tary risk assessments for pesticides (Durango Software, 2011). Chronic dietary consumption data for all fruit and vegetable commodities by the general U.S. population were extracted from the model.

The USDA Pesticide Data Program (PDP) is a market basket survey of pesticide residues that is performed annually by the USDA (USDA, 2011). Five recent years of available data were used for this analysis (2004–2008). To ease the burden of calculation, the analysis was restricted to pesticides that accounted for at least 0.05% of the total number of detections. This resulted in a list of 136 pesticides, accounting for about 98.5% of the total detections. The PDP program includes only certain commodities, whereas the intent of this analysis is to estimate exposure from all fruit and vegetables. Therefore, the available PDP data were assigned as surrogates for related commodities using standard EPA practice for pesticide dietary risk assessments (e.g., carrot data were assigned to all root vegetables, banana data were assigned to plantains, etc.). Table 2 summarizes the surrogate matching. Using this approach, the PDP data were assigned to sufficient surrogate commodities to account for 99.3% of average daily vegetable consumption and 96.1% of average daily fruit consumption.

The cancer classifications and Q_1^* values of currently registered pesticides were obtained from a database provided by the EPA for current use pesticides (U.S. EPA, 2010). The Q_1^* values are summarized in Table 3. There are some pesticides that are classified as "possible human carcinogens" for which the EPA has concluded that a reliable quantitative assessment of cancer risk is not possible at this point in time. These pesticides are not included in this analysis, consistent with the EPA risk assessment methods for pesticides. Also, the EPA has concluded that some potentially carcinogenic pesticides have non-linear dose–responses and that risks can be estimated with a threshold approach. In these cases, cancer risk estimates are assumed to be negligible for dietary exposure which is a very small source, consistent with the EPA dietary risk assessment methods. Some pesticides detected in the PDP are not currently registered for legal use. For example, DDT and dieldrin are still present in the environment due to long persistence, despite being banned in the U.S. in the 1970s and 1980s, respectively. In these cases, Q_1^* values were obtained from the EPA's Integrated Risk Information System (IRIS). A total of 21 pesticides (including metabolites and isomers analyzed separately) classified as carcinogens have available Q_1^* values.

The Q_1^* values for the pesticides included in this analysis range from 0.000875 (mg/kg/d)$^{-1}$ (carbaryl) to 16 (mg/kg/d)$^{-1}$ (dieldrin). The highest Q_1^* values are for the organochlorine pesticides that are no longer registered in the United States, including chlordane, dieldrin, DDT (including metabolites), and hexachlorobenzene. To facilitate the analysis, thiacloprid (Q_1^* = 0.0406 (mg/kg/d)$^{-1}$) was selected as the index chemical, and Potency Adjustment Factors (PAFs) were estimated for all other chemicals as the ratio of the Q_1^* for each chemical to the index value of 0.0406 (mg/kg/d)$^{-1}$. Dietary exposures were then calculated on a thiacloprid-equivalent basis for each commodity–pesticide combination using the commodity average daily consumption (mg/kg bw/day), average pesticide residue concentration from PDP data (calculated assuming zero residues for all non-detect samples) and the PAF for that pesticide. The resulting thiacloprid-equivalent exposure estimates for all commodity–pesticide combinations were then summed to yield a total exposure estimate. This procedure is mathematically equivalent to performing the assessment for each chemical separately and adding up the risks.

To account for the small fraction of commodities where surrogate PDP data were not available, the estimated total exposures were adjusted upward by dividing by the fraction of consumption for which surrogate PDP data were available (99.3% for vegetables and 96.1% for fruit).

The final step was to estimate the number of cancer cases that could be attributed to increased consumption of one 80 g serving each of fruit and vegetables containing pesticide residues. First, the total adjusted thiacloprid-equivalent exposure (in mg/kg/day) was multiplied by the Q_1^* for thiacloprid to estimate the cancer risk from lifetime consumption of all fruits and vegetables. Next, the average daily consumption of fruit and vegetables (4.363 and 4.310 g/kg bw/day, respectively) was multiplied by the average body weight for the U.S. population (including children) of 54.05 kg (derived from DEEM–FCID analyses by comparing the average daily consumption estimated with and without dividing by body weight), resulting in average daily consumption estimates of 236 g/day for fruit and 233 g/day for vegetables. From the associated cancer risk for these average daily consumption estimates, it was a straightforward matter to estimate the increased cancer risk associated with an additional 80 g consumed daily. Multiplying this cancer risk by 155 million people (the half of the population assumed to increase consumption by 80 g/day) yields total increased lifetime cancer cases. The above result was divided by a 70 year lifetime (the standard assumption for cancer risk assessment) to annualize the estimate.

3. Results

3.1. Cancer prevention benefits of fruit and vegetable consumption

Table 1 shows the estimated number of avoided cancer cases for each consumption–cancer type combination based on Eq. (2). The estimated avoided cases range from 203 (stomach cancer and non-starchy vegetables, cohort studies) to 21,958 (lung cancer and fruits, case control studies; the result for lung cancer and fruits for cohort studies was 6112 avoided cases). The avoided cases across the categories in Table 1 cannot be readily summed. Also, the results for case control and cohort studies for the same commodity–cancer type pair cannot be summed. Table 1 includes some results for subtypes of fruits and vegetables, which cannot be easily summed with a study that considered all fruits or all vegetables. However, summing across the cancer types is valid. The sum using the average result across each cancer type is 29,441 avoided cases per year. The sum using the average result across each cancer type and using the likely more reliable result from the cohort studies for lung cancer (the outlying value in the dataset is the RR for lung cancer for case control studies) is 21,518 cases per year. Thus, a rounded lower-bound estimate is taken as approximately 20,000 avoided cancer cases per year if one-half the population increases fruit and vegetable consumption by one serving per day. The number is rounded to avoid conveying unwarranted precision in the calculation. This estimate may be conservative given that there may be separate effects for fruits and vegetables, but we averaged across the estimates. We did not consider avoided cases for prostate cancer associated with lycopene, because it would have required making an assumption about increases in specific foods. On the other hand, except for the outlying value for lung cancer, we included the case control study results, which mostly, but not always, gave somewhat higher values. The case control results were included, except for lung cancer where the case control studies had a substantially more protective effect than the cohort studies, because cohort study results were not always available (e.g., esophageal cancer). Also, several of the relative risk estimates had confidence intervals that overlapped with 1.0 (just barely), indicating a lack of statistical significance. We included all of the estimates for food type-cancer type combinations considered "probable" by WCRF/AICR, but the results were very similar with or without including relative risks with confidence intervals overlapping 1.0.

3.2. Upper-bound estimate of cancer cases caused by pesticide residues

The total estimated thiacloprid-equivalent exposure for the increased serving of fruits and vegetables was 3.8×10^{-5} mg/kg bw/day for fruits and 2.1×10^{-4} mg/kg bw/day for vegetables. The total estimated lifetime cancer risk for all chemicals combined was 1.5×10^{-6} for fruits and 8.5×10^{-6} for vegetables. The additional cancer cases per year potentially attributed to increased consumption of fruit and vegetables containing pesticide residues is 1.2 cases per year for fruit and 6.5 cases per year for vegetables, for a total of 7.7. As with the cancer prevention estimate, we submit the result is best reported as a round number to avoid portraying an unintended level of precision. Thus, as a round number, the total number of estimated cases is approximately 10 per year. For reasons discussed below, this estimate should be regarded as an upper-end estimate due to the methods in which Q_1^*s are estimated.

About one-half of the estimated cancer risk is due to dieldrin, which is an organochlorine pesticide that has been banned since the 1980s but is still present on food due to its persistence in the environment.

It is notable that the benefit estimate from the epidemiologic data essentially includes a net benefit of cancer prevention benefits minus pesticide cancer risks. However, since the cancer risk estimate is orders of magnitude smaller, it is not necessary to adjust the benefit estimate within the precision that it is presented.

4. Discussion

The estimates provided in this analysis make a number of assumptions and use data and methods of varying reliability.

The cancer prevention analysis relies on a meta-analysis of nutritional epidemiology studies conducted by the WCRF/AICR (WCRF/AICR, 2007). The associations included in this analysis were ones considered "probable" by the WCRF/AICR. A significant strength of these data is that the underlying epidemiologic studies are observations of the population that divide the groups by their fruit and vegetable consumption. Therefore, it is not necessary to extrapolate the results of the studies to a population with significantly different exposure, as is the case with the high dose rodent studies that are the basis for the cancer risk estimates for pesticides. However, confounding can be a significant problem in epidemiologic studies and, in some cases, part of the difference in cancer rates between populations with differing fruit and vegetable intake may be the result of insufficient controls for confounding factors. Nonetheless, numerous studies with differing methods were included in the WCRF/AICR meta-analysis, which minimizes the extent to which the associations are due to confounding.

Some researchers currently view the association between fruit and vegetable consumption and cancer prevention as less than "probable," the classification used by WCRF/AIRC. Key (2011) reviewed the available evidence and concluded that the only consistent association was for oral cavity, pharynx and esophageal cancers, though even these associations could be due to residual confounding. Key (2011) concluded that the association for colorectal and lung cancer was weak and inconsistent. Key (2011) also noted that the strongest associations between fruit and vegetable consumption and cancer are for cancers that are strongly associated with tobacco use. For lung cancer, the fruit and vegetable benefit seems to be restricted to those with a history of smoking. These findings raise the possibility that smoking is a confounder for the fruit and vegetable associations.

Complementing the epidemiologic studies, there is a body of mechanistic evidence that select components of fruits and vegetables, including carotenoids, lycopene, folic acid, and Vitamin C, may reduce the initiation or progression of certain tumors (Gold et al., 2001; Sharoni et al., 2011; Lin et al., 2011; Gao et al., 2007).

Boffetta et al. (2010) recently published the largest study yet to evaluate the potential protective effect of fruit and vegetable consumption for cancer. This study included nearly half a million subjects in Europe and evaluated all cancer types only. The study found a small (2–3%) but statistically significant protective effect for fruit and vegetable consumption and overall (all type) cancer incidence. The small effect size led some to question whether the positive effects of fruits and vegetables for cancer prevention have been overstated (Willett, 2010). However, Bouchardy et al. (2011) noted that the effects may be stronger for selected cancer types. By combining all cancer types, the effects in Boffetta et al. (2010) were diluted. The current study only included benefits from a few cancer types for which there is good evidence for a benefit for fruit and vegetable consumption. Overall, our results are consistent with Boffetta et al. (2010). Boffetta et al. (2010) states that with an "average [fruit and vegetable consumption] increase of approximately 150 g/d, 2.6% cancers in men and 2.3% cancers in women could be avoided." Considering all cancer types, the U.S. rates are 541.8 per 100,000 for men and 417.3 per 100,000 for women (National Cancer Institute, 2012). Applying the Boffetta et al. (2010) result to half the U.S. population would lead to 18,356 avoided cases for a 150 g/day increase in fruit and vegetable consumption. This result is very similar to our estimate of 20,000 avoided cases for an 80 g/day increase in fruit and vegetable consumption each (a total of 160 g/day).

The WCRF/AICR found limited evidence of cancer prevention for fruits and/or vegetables for certain cancer types, including cancer of the nasopharynx, colorectum, ovary, endometrium, cervix, prostate, and liver. If fruit and vegetable consumption does reduce the risk for these cancers, the analysis provided in the current paper may underestimate the true cancer prevention benefits of fruits and vegetables.

There are significant uncertainties associated with the estimates of cancer risk from pesticides. As the EPA states in its guidelines, its estimates for cancer risk "while uncertain, are more likely to overstate than understate hazard and/or risk" (U.S. EPA, 2005). The major limitation in the cancer risk estimates is that they rely on testing in rodents. Rodent cancer assays involve dosing animals with chemicals at levels far beyond the exposure levels that people are likely to experience, particularly from dietary exposure to pesticides. The high doses are required in order to detect tumors using the small sample sizes in these studies (typically 50 animals per dose group). The risks at the high doses are typically mathematically extrapolated to lower doses using the linearized multistage dose–response model (Crump, 1996). The EPA stated in its previous carcinogen risk guidelines that estimates from the linearized multistage model do "not necessarily give a realistic prediction of risk. The true value of the risk is unknown, and may be as low as zero" (U.S. EPA, 1986). As an example, the Q_1^* for permethrin is based on mouse lung combined adenomas and carcinomas and the lowest dose tested was 3 mg/kg bw/day (U.S. EPA, 2004). The total permethrin exposure in the present analysis was 1.3×10^{-4} mg/kg bw/day. Thus, the lowest dose where tumors were observed was more than 20,000 times higher than the estimated dose in this analysis. As another example, the Q_1^* for diuron is based on kidney carcinomas in male rats. Tumors were only observed in the highest dose group of 600 mg/kg bw/day (U.S. EPA, 2011a). The estimated diuron dose in this analysis was 8.7×10^{-9} mg/kg bw/day, or about 70 billion-fold lower than the highest dose were tumors were detected (Note: diuron residues contributed negligibly to the cancer risk in the present calculation).

Some researchers have been sharply critical of the use of rodent assays for cancer (Ames and Gold 1990 and Ames et al., 1993), arguing that the high doses typically used in these studies yield

results that are limited with respect to their practical relevance. For example, the high doses may cause chronic wounding of tissues, cell death, and chronic cell division of neighboring cells to replace the damaged tissue. Because dividing cells are more vulnerable to the effects of toxicants, such a scenario can lead to development of cancer that might not occur at lower doses. It has also been argued that about 99.99% of the pesticides that Americans consume in their diet are of natural origin, produced by plants as part of their natural defense mechanisms against fungi, insects and other animal predators (Ames et al., 1990). Only a small number of these natural pesticides have been tested in rodent assays, but more than half were positive (Gold et al., 2001). Yet, as discussed above, people who eat the most fruits and vegetables generally have lower rates of cancer. This observation supports the view that the pesticide rodent carcinogen assays are not reliable predictors of cancer for dietary pesticide exposure.

For some of the pesticides considered in this analysis, there is evidence contrary to EPA's carcinogen classification. For example, a study of 570 workers at a production plant that produced dieldrin between 1954 and 1970 found no association between exposure and cancer mortality (Van Amelsvoort et al., 2009). The average dieldrin exposure in this population was 737 mg over their employment, whereas the lifetime estimated exposure in the present analysis was 0.6 mg. As noted earlier, in our current study dieldrin contributed about half of the cancer risk. Another analysis of this cohort concluded that the cancer incidence was inconsistent with animal data used in the EPA risk assessment that the Q_1^* is based upon (Sielken et al., 1999). Similarly, there was no clear association with cancer and organochlorine pesticides in the Agricultural Health Study, a cohort study of over 50,000 licensed pesticide applicators in Iowa and North Carolina (Purdue et al., 2007).

One potential source of underestimation in the cancer risk estimates is the assumption that non-detect residues can be counted as zero. This assumption was necessary because the number of detections is very small when considering all combinations of commodities and pesticides. Therefore, using a traditional assumption such as assuming half the limit of detection for all non-detects would substantially increase the assumed level of the residues and yield exposures estimates 25-fold or more greater than assuming zero for non-detects. EPA similarly counted non-detects as zero in its cumulative risk assessment for organophosphates (U.S. EPA, 2011b).

Another potential source of underestimation is that some pesticides that are considered "possible" carcinogens by EPA were not included in this analysis because quantitative estimates of cancer risk are not possible. However, we suggest this potential problem was balanced in the present analysis by excluding the anticancer benefits for cancer types for which WCRF/AICR found only "limited evidence."

Comparing the reliability of the respective set of estimates, it should be noted that the nutritional epidemiology studies provide a central estimate (or "mostly likely estimate") of benefit from a human population, whereas the cancer risk estimates rely on an extrapolation of risk from high doses in rodent studies to substantially lower doses in the diet of humans.

The estimates provided in the current analysis are based on long-term consumption of fruits and vegetables; and, therefore, do not represent an instantaneous change if one-half of the population did indeed increase its fruit and vegetable consumption by one serving per day. The cancer risk estimates assume lifetime exposure to the increased pesticide residues, and the estimate would be lower for less than lifetime exposure. The duration of increased consumption of fruits and vegetables needed to reduce cancer risk is less clear, but certainly long-term change is needed.

In closing, it is important to note that in the current study the focus of our attention was on the potential impact of fruit and vegetable consumption on the risk for cancer. We recognize that the amount of fruit and vegetable consumption in one's diet may also be linked with the risk for certain vascular diseases. However, similar to the potential influence of fruits and vegetables on the risk for cancer, literature on the influence of these foods on vascular health is complicated (Dauchet et al., 2009); it is our intention that this issue will be a subject of a future paper. Finally, with respect to the broad area of diet and health, the importance of risk–benefit considerations are not unique to fruits and vegetables and pesticide residues. Within the Sixth Framework program of the European Commission the BRAFO (Benefit–Risk Analysis for Foods) project is designed to develop methods for the quantitative comparison methods of the human health risks and benefits of select foods and food components (Hoekstra et al., in press). An example of the above is salmon. While it can be a rich source of omega-3 fatty acids, it can also contain significant amounts of environmental toxicants. A BRAFO-tiered approach has recently been used to analyze the relative risks and benefits of diets rich in salmon (Watzl et al., in press). In conclusion, a major goal of public health programs in nutrition is to assist health professionals in the development of dietary recommendations for the general population. It is submitted that the success of such programs will be dependent in part on a better understanding, by the general public, as well as health professionals, of the basic concepts and implications of risk benefit analysis.

5. Conclusions

Based on the analysis presented in the current paper, if one-half of the U.S. population were to increase fruit and vegetable consumption by one serving each per day, an estimated 20,000 cancer cases might be avoided each year. In contrast to this predicted reduction in cancer cases, the pesticide residues on those fruits and vegetables might result in up to about 10 additional cancer cases per year, While both of these estimates have high uncertainties, the orders of magnitude difference between the benefit and risk estimates strongly supports the conclusion that the positive health effects that could result from an increased consumption of fruits and vegetables will greatly exceed any putative negative effects that might be associated with the increased intake of pesticide residues on fruits and vegetables. Surveys suggest that many, if not most, consumers do not appreciate the above relative differences in the risk, versus the benefits, of increasing their intakes of fruits and vegetables. The extent to which consumer fears over pesticide residues reduce the motivation for increasing fruit and vegetable consumption is an area of active debate, however survey data suggests it is not insubstantial. Educational materials and programs aimed at improving the typical consumers understanding of risk–benefit concepts could provide a number of important public health benefits.

Conflicts of Interest

This study was sponsored by the Alliance for Food and Farming, which includes members in the farming industry. The authors have done consulting work with agrochemical companies.

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