

## Can pure fruit and vegetable juices protect against cancer and cardiovascular disease too? A review of the evidence

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While it is widely accepted that fruit and vegetables (F&V) lower the risk of cancer, and cardiovascular disease (CVD), the role of pure fruit and vegetable (PFV) juices is often downplayed. This review poses two questions: Are the protective benefits of F&V dependent upon constituents lacking in PFV juices (e.g. fibre)? Do PFV juices impact on disease risk when considered separately from F&V? Studies comparing the effects of fibre and antioxidants were reviewed, yielding the finding that the impact of F&V may relate more strongly to antioxidants, than to fibre. For the second question, high-quality published studies that considered PFV juices were reviewed. The impact of PFV juices on cancer risk was weakly positive, although a lack of human data and contradictory findings hampered conclusions. For CVD, there was convincing evidence from epidemiological and clinical studies that PFV juices reduced risk via a number of probable mechanisms. It was concluded that the view that PFV juices are nutritionally inferior to F&V, in relation to chronic disease risk reduction, is unjustified.

**Keywords:** *Pure juice, cardiovascular disease risk, cancer risk*

### Introduction

A diet that is rich in fruits and vegetables (F&V) has been associated with protection against cardiovascular disease (CVD) (Bazzano et al. 2002) and several common cancers (van't Veer et al. 2000). Although F&V contain a range of vitamins, minerals and trace elements, it is commonly proposed that the active components, in relation to chronic disease prevention, are likely to be soluble fibre and/or one or more antioxidants. Despite considerable research to identify which antioxidants might impact most favourably, there is no consensus view. Supplementation studies on  $\beta$ -carotene, vitamin C and vitamin E have so far yielded disappointing results (Stanner et al. 2003).

Epidemiological studies in the past often failed to differentiate between the effects of whole F&V and the juices of these. Thus, information on whether pure fruit and vegetable (PFV) juices possess similar protective attributes to whole F&V is only just emerging. Some dietary policies have downplayed the role of PFV juices by suggesting that these fail to provide the same nutritional benefits as whole F&V. The UK Food

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Standards Agency (2004) counts PFV juice as one portion of F&V regardless of how much is drunk, while US dietary recommendations (Department of Health and Human Services, and Department of Agriculture 2005) claim that ‘juice is generally less desirable because it has less fiber’. The World Cancer Research Fund (1997) makes a similar comment, although the World Health Organisation’s (2003) recommendations on cancer and CVD prevention do not differentiate between PFV juices and whole F&V. The US Food and Drug Administration (2002a) approved a health claim that F&V reduce low-density lipoprotein (LDL) levels but only if they ‘contain fiber’. A further US health claim, relating to the anti-hypertensive properties of potassium, does apply to PFV juices (US Food and Drug Administration 2002b).

While it is true that most PFV juices are deficient in fibre, other important preventative nutritional components, such as antioxidants and folate, are present in both whole and juiced F&V (Lugasi and Hovari 2003). Two questions are pertinent: Are the protective benefits of whole F&V for chronic diseases owed mainly to constituents not present in PFV juices (i.e. soluble fibre)? Do PFV juices impact on chronic disease risk when considered separately from whole F&V? We will address these issues, in relation to cancer and CVD, using a systematic review of the evidence.

### **Dietary intakes of juices**

Nearly 60% of adults consume PFV juices, and sales of these increased between 1999 and 2004 by 15% (MINTEL 2004). The UK National Diet and Nutrition Survey (Henderson and Gregory 2002) reported that average consumption of PFV juices was 106 g/day, with men consuming slightly more than women. Intakes peak among those aged 25–34 and thereafter decline with age (MINTEL 2004). The prime drivers behind the current growth in consumption include healthy eating trends and a desire to consume more natural products (MINTEL 2004). Increased awareness of the ‘5-a-day’ message and the dominance of soft drinks over the more traditional tea and coffee may also play a part.

PFV juices are rich sources of nutrients such as vitamins, minerals, trace elements and soluble fibre (the latter only in juices with ‘bits’). Depending on the type of juice, a range of phytochemicals (e.g. polyphenols, especially flavonoids) may also be present. These have been implicated in the prevention of cancer and CVD.

### **Bioavailability and the impact of processing**

The antioxidant profile of PFV juices is complex and includes carotenoids (e.g. lycopene,  $\beta$ -carotene), tocopherols and ascorbic acid, as well as polyphenols (Lugasi and Hovari 2003). These should be considered as a whole when assessing the potential antioxidant activity of PFV juice, since antioxidants may act synergistically rather than individually.

Some commercial juice drinks contain added vitamins such as vitamin C, vitamin E and several of the B vitamins. However, in spite of a relatively high vitamin content, the antioxidant capacity of such products was found to be weak when studied using *in vitro* techniques (Lugasi and Hovari 2003). This implies that, in PFV juices, polyphenols are the most active antioxidants. Polyphenol content varies between

Table I. Effect of processing on fruit and vegetable juices.

Type of fruit/ vegetable juice	Effect of processing on phenolic compounds and antioxidant activity
Orange (Gil-Izquierdo et al. 2002)	Commercial squeezing extracted 22% more phenolic compounds than hand squeezing. No loss of phenolic compounds detected with pasteurization or concentration. Losses occurred during freezing and thawing Mild pasteurization, standard pasteurization, concentration and freezing did not affect the total antioxidant capacity of juice. However, they did have an effect in pulp, where it was reduced by 47%.
Apple (van der Sluis et al. 2002)	Raw juice had an antioxidant activity that was only 3–10% of the activity of fresh apples Enzymatic treatment and aeration of the pulp to increase higher juice yield in commercially available juice lower polyphenol concentrations and, thus, antioxidant capacity
Tomato (Gahler et al. 2003)	Loss of vitamin C shown during production of juice Significant increase in phenolic compounds during processing Antioxidant capacity increased after homogenization and decreased after sterilization and bottling
Pomegranate (Gil et al. 2000)	Antioxidant activity higher in commercial juices extracted from whole pomegranates compared with hand squeezing

PFV juices, with the highest levels seen in blackcurrant (909–1228 mg/l) and red grape (137–980 mg/l) juices (Lugasi and Hovari 2003).

Studies have investigated the effects of processing on a number of different PFV juices, particularly the impact on antioxidant activity and levels of phenolic compounds. A summary of the results is presented in Table I. Commercial squeezing of orange juice extracted one-fifth more phenolic compounds than hand squeezing (Gil-Izquierdo et al. 2002), and commercial pomegranate juice had a greater antioxidant activity than hand-squeezed juice (Gil et al. 2000).

Pasteurization of the pulp during the processing of orange juice causes vitamin C levels to drop by around 60% and nearly halves antioxidant capacity (Gil-Izquierdo et al. 2002). However, these losses do not greatly influence the overall vitamin C content of commercially produced whole juice because pulp is present at low concentrations (a maximum of 10% by volume).

A major problem with apple juice processing is that most of the antioxidant compounds are absorbed into the solid matter in the pomace (the waste product from apple juice production) and are thus not transferred to the final juice (van der Sluis et al. 2002). Techniques are now being developed to extract antioxidants from the pomace and add them at a later stage to the apple juice product. It would seem that current methods of apple juice production severely limit the potential health benefits.

Tomatoes and related products have been studied extensively due to the positive impact of lycopene on prostate cancer risk. Agarwal et al. (2001) conducted an analysis of the stability, bioavailability and antioxidant potential of lycopene. These remained constant during the production of tomato juice for up to 12 months. Interestingly, availability of lycopene in tomato juice increased during cooking,

especially in the presence of oil. This was probably due to the formation of the *cis*-isomeric form of lycopene.

These findings demonstrate that processing can impact on levels of phenolic compounds, bioavailability and overall antioxidant activity in the final juice product. However, it is clear that PFV juices still possess considerable antioxidant potential.

### **Are benefits of F&V due to fibre or antioxidants?**

If PFV juices are, indeed, less nutritionally active in chronic disease prevention than whole F&V, one would expect the evidence for soluble fibre to be more robust than for antioxidants. Some authors have attempted to address the individual effects of fibre and fruits/vegetables using epidemiological methods. In a review of the evidence for cancer prevention, Smith et al. (1999) argued that carotenoid-rich F&V possessed anticancer properties even when the influence of fibre was excluded. Using a matched case–control study of acute myocardial infarction incidence, Martinez-Gonzalez et al. (2002) found an inverse association between fibre intake and incidence of myocardial infarction, but also a separate inverse association with fruit, but not vegetable, intake. This finding was supported by a meta-analysis of cohort studies of CVD (Law and Morris 1998) that reported inverse associations between CVD and each of the following: fruit fibre, vegetable fibre, vitamin C and carotenoids. All were of a similar magnitude. A study of breast cancer risk (Verhoeven et al. 1997) found no significant effects for fibre, antioxidants, fruits or vegetables. Jenkins et al. (2000) questioned whether the apparent benefits of fibre-rich foods in improving CVD risk factors (e.g. clotting, insulin sensitivity, LDL cholesterol) may be due to their low glycaemic indices, rather than fibre *per se*.

Much experimental work has been carried out on both fibre and antioxidants. Using animal *in vitro* and *in vivo* protocols, antioxidants have been found to scavenge free radicals, reduce LDL oxidation, stimulate the immune system, decrease platelet aggregation, alter cholesterol metabolism, lower blood pressure and modulate detoxification enzymes (Lampe 1999; Mojzisova and Kuchta 2001; Heber and Lui 2002).

Work on fibre has suggested that insoluble, rather than soluble, fibre is the major protective influence for colo-rectal cancer (Harris and Ferguson 1993). Indeed it has been postulated that some forms of insoluble fibre may enhance carcinogenesis (Harris and Ferguson 1999). An exception is pectin, which appears to inhibit rat colonic proliferation (Umar et al. 2003). Pectin is present in both whole fruits and juices (Yen and Lin 1998).

It is certainly difficult using the available literature to make an objective comparison between the merits of soluble fibre and antioxidants in cancer and CVD risk reduction (Harris and Ferguson 1993). However, two important points arise; the epidemiological evidence suggests benefits for both fibre and non-fibre constituents of F&V, while the experimental evidence leans towards antioxidants, particularly in the identification of plausible mechanisms. Taking these points together, one could argue that the evidence for antioxidants is more robust. At the very least, soluble fibre does not appear to have a distinct advantage over those constituents of F&V that could reasonably be found in PFV juices.

## Do fruit and vegetable juices impact on chronic disease?

In order to address this question, we searched the Cochrane Library and MEDLINE for studies relating to PFV juices and cancer/CVD risk. Search criteria are presented in Appendix 1. This process was supplemented with a check of reference lists to address any gaps. Animal studies were excluded and the research had to consider PFV juices (not supplements). We included both freshly squeezed juices and those made from 100% concentrate (reconstituted to their original strength after transportation). We excluded commercial juice drinks and smoothies. Where studies reported data on PFV juices as part of overall F&V consumption, results had to be clearly differentiated to consider the data on juices separately. Independent guidelines for the assessment of methodological quality (Scottish Intercollegiate Guidelines Network 2005) were adapted to include epidemiological evidence and studies using *ex vivo* techniques (see Appendix 2). These were used to guide the relative value placed on studies. The purpose of this was to increase the transparency and reproducibility of the conclusions and limit any investigator bias.

### Potential impact on cancer

Eleven studies were located and are described in Table II. Three epidemiological studies looked at breast cancer and F&V consumption, including a separate analysis of PFV juice (Smith-Warner et al. 2001; Olsen et al. 2003; Van Gils et al. 2005). No significant associations were observed between PFV juice intake and breast cancer risk. This agrees with Verhoeven et al. (1997), who found no effects for whole F&V or their components.

One study suggested a greater risk of renal cell carcinoma (RCC) in males only with increasing consumption of PFV juices (Handa and Kreiger 2002). In the Rashidkhani et al. (2005) study, there was a suggestion of increased risk in women but it was not statistically significant. Both studies suggested that consumption of whole F&V was associated with reduced risk of RCC. Neither study specified the types of juices consumed so it is difficult to identify a mechanism. Other risk factors for RCC such as obesity, smoking and inactivity may have influenced the findings, and further investigation is required.

In cancers other than breast cancer and RCC, the number of studies looking at the effects of PFV juices was limited to one per site and, as such, no conclusions could be drawn. However, it was interesting to note in the study by Giovannucci et al. (1995) that tomato juice did not appear to impact on prostate cancer risk. This is probably because lycopene in tomato juice has a low bioavailability until cooked or mixed with oil (Agarwal et al. 2001).

Three clinical studies were located that examined the effects of PFV juices on DNA damage in humans. It has been suggested that dietary factors that limit free radical attacks on DNA are likely to protect against cancer. Two of the studies were conducted by staff from one laboratory, although 6 years apart. In all three studies, differing juices were used; grape (Park et al. 2003), mixtures of juices rich in polyphenols (Bub et al. 2003), and carrot, tomato and spinach (Pool-Zobel et al. 1997). All found significant reductions in lymphocyte DNA damage.

In conclusion, it is evident that polyphenols and other antioxidant compounds found in PFV juices exert cancer-protective effects via a decrease in oxidative and other damage to DNA. However, the clinical data are insufficient at present to assert

Table II. Pure fruit and vegetable juices and cancer.

Reference	Subjects	Study details	Outcomes
<b>Chronic disease</b>			
Hung et al. (2004)	Nurses Health Study, $n = 71,910$ women; Health Professionals Follow-Up Study, $n = 37,725$ men	Baseline semi-quantitative FFQ Participants followed up for CVD incidence (1964 events), cancer (6584 events) or death (787)	No statistical significant reduction in risk of major chronic disease associated with consumption of citrus fruit or their juices
<b>Breast cancer</b>			
Van Gils et al. (2005)	EPIC Study, $n = 285,526$ women, 25–70 years old	Dietary questionnaire in 1992–1998. Follow-up for incidence of cancer until 2002. $n = 3659$ invasive breast cancer cases	No significant associations between vegetable or fruit juice intake and breast cancer risk Relative risk for the highest vs the lowest quartile were 1.05 (95% confidence interval, 0.92–1.2)
Olsen et al. (2003)	$n = 23,798$ postmenopausal women, Denmark	$n = 425$ cases of primary breast cancer diagnosed	Fruit and vegetable juice not associated with breast cancer incidence Beneficial association found for oestrogen receptor-negative, breast cancer and fruit juice (not significant)
Smith-Warner et al. (2001)	Pooling study, $n = 351,825$ women	Diet analysed at baseline by FFQ $n = 7377$ cases invasive breast cancer occurred	Fruit juice not associated with breast cancer risk (vegetable juice data not separated from total vegetables) Relative risk for highest vs lowest quartile compatible with a reduced risk for fruit juice but not statistically significant 1.00 (95% confidence interval, 0.95–1.06)
<b>Colon cancer</b>			
Briviba et al. (2004)	$n = 22$ healthy men on low-carotenoid diets	RCT for 2 weeks using 330 ml/day tomato juice or carrot juice Antioxidant capacity assessed	Consumption of both juices increased carotenoid level in plasma and faeces ( $P < 0.001$ ). Antioxidant capacity of LDL increased by $\sim 4.5\%$ ( $P = 0.08$ ). Lipid peroxidation not affected
<b>Colorectal cancer</b>			
Smith-Warner et al. (2002)	Minnesota Cancer Prevention Study: $n = 564$ adenomatous polyps cases, $n = 682$ colonoscopy negative controls, $n = 535$ community controls	Diet followed up using FFQ	In women, adenoma risk halved in highest versus lowest quintile of juice consumption (cases vs colonoscopy-negative controls, odds ratio = 0.50, 95% confidence interval = 0.27–0.92; cases vs community controls, odds ratio = 0.56, 95% confidence interval, 0.3–1.06). No association with risk in men

Table II (Continued)

Reference	Subjects	Study details	Outcomes
<b>Prostate cancer</b>			
Giovannucci et al. (1995)	Health Professionals Follow-Up Study, $n = 47,894$ subjects initially free of cancer	Prospective cohort study. Dietary intake assessed over 1-year period Follow-up questionnaires in 1988, 1990, 1992 $n = 812$ new cases of prostate cancer	Tomato juice unrelated to risk of prostate cancer but whole tomatoes and cooked tomato significantly and inversely associated
<b>Renal cancer</b>			
Rashidkhani et al. (2005)	$n = 61,000$ women, 40–76 years old, Sweden	Population-based prospective cohort study with 13.4 years follow-up $n = 122$ cases of renal cell carcinoma	Non-significant trend for positive association between fruit juice and renal cell carcinoma ( $p = 0.10$ )
Handa and Kreiger (2002)	$n = 461$ cases (210 women) of renal cell carcinoma aged 20–74	Cases and controls mailed self-administered FFQ	Risk of renal cell carcinoma positively associated with increasing fruit juice intake in males (odds ratio = 1.8, 95% confidence interval = 1.0–3.1)
<b>DNA damage</b>			
Park et al. (2003)	$n = 67$ healthy adults	480 ml grape juice given daily for 8 wk	Grape juice consumption resulted in significant decrease in lymphocyte DNA damage
Bub et al. (2003)	$n = 27$ healthy men	RCT over 10 weeks using apple, mango or orange juice plus: Juice A, anthocyanin-rich fruit juice; Juice B, flavonoids-rich green tea, lime and apricot	Ingestion of juices significantly reduced TBARS. Antioxidant power measured by FRAP did not change, although there was a trend towards increased antioxidant power ( $p = 0.07$ ) after Juice B
Pool-Zobel et al. (1997)	$n = 23$ non-smoking men	Three different carotenoid rich juices were given for 2 weeks each (tomato, carrot and spinach)	Significant decrease in endogenous levels of strand breaks in lymphocyte DNA Oxidative base damage significantly reduced during carrot juice intervention

RCT, randomized controlled trial; FFQ, food frequency questionnaire; FRAP, ferric reducing ability of plasma assay; TBARS, thiobarbituric acid reactive substances assay.

that consumption of PFV juices can reduce cancer risk. Long-term human supplementation studies are needed, although it is acknowledged that the duration of cancer development and its multi-factorial nature makes it a particularly difficult area in which to confirm *in vitro* results.

### **Potential impact on cardiovascular disease**

We found 37 studies relating to CVD and the consumption of PFV juices. These were subdivided into ischaemic stroke, platelet aggregation, antioxidant capacity, serum lipoprotein levels and plasma homocysteine levels (see Table III).

#### *Chronic disease*

The study by Hung et al. (2004) found no statistically significant reduction in the development of CVD with increased consumption of citrus fruit juices or with whole citrus fruit. The impact of other PFV juices was not examined. The lack of a significant association for whole F&V with such a large sample size is unexpected, although the authors reported a weak inverse trend.

#### *Ischaemic stroke*

Three studies were located. The randomized controlled study demonstrated a reduction in blood pressure in hypertensive subjects given Concord grape juice over a placebo drink (Park et al. 2004). The two epidemiological studies reported conflicting results; a Danish study of 54,000 subjects (Johnsen et al. 2003) found no statistically significant benefit for PFV juices, while the Nurses' Health Study of 75,000 women (Joshipura et al. 1999) found that citrus fruit juice was protective against the risk of ischaemic stroke.

#### *Platelet aggregation*

Seven studies were found. The *in vitro* studies found anti-platelet activity for a number of PFV juices, particularly tomato, grapefruit, melon and strawberry (Dutta-Roy et al. 2001). The relationship appeared to be dose-dependent (Lazarus and Garg 2004).

A double-blind parallel trial was conducted on patients with type 2 diabetes or impaired glucose tolerance comparing tomato juice with a placebo (Lazarus et al. 2004). Platelet aggregation decreased in the tomato juice group and remained significantly lower than baseline after 3 weeks, which indicates that the *in vitro* anti-platelet actions of PFV juices translate to the clinical environment.

The remaining four studies examined the effect of purple grape juice on platelet aggregation in healthy human subjects, finding a significant reduction in three studies. Three of these compared purple grape juice with other beverages (e.g. orange juice, grapefruit juice, red wine and white wine), finding the strongest anti-platelet effects for purple grape juice, with red wine also showing significant effects. This is perhaps unsurprising given the commonality between these beverages. The fourth study found no effects on platelet aggregation for any of the juices studied (Pace-Asciak et al. 1996) but has been criticized for using less sensitive measurement techniques (Folts 2002).

Table III. Pure fruit and vegetable juices and cardiovascular disease.

Reference	Subjects	Study details	Outcomes
<b>Chronic disease study (one study)</b>			
Hung et al. (2004)	Nurses Health Study, $n=71,910$ women; Health Professionals Follow-Up Study, $n=37,725$ men	Prospective cohort study, semi-quantitative FFQ; 14 year follow-up yielding 1964 CVD events, 6584 cancers, 787 deaths	Citrus fruit juices not associated with chronic disease risk
<b>Ischaemic stroke (three studies)</b>			
Park et al. (2004)	$n=40$ hypertensive subjects, Korea	8-week double-blind RCT: 5.5 ml/kg/day Concord grape juice, or \Calorie-matched placebo drink	Systolic blood pressure reduced by 7.2 mmHg ( $p=0.005$ ). Diastolic blood pressure reduced by 6.2 mmHg ( $p=0.001$ )
Johnsen et al. (2003)	Danish Diet Cancer and Health Study, $n=54,506$ adults	Prospective cohort study yielding $n=266$ cases ischaemic stroke	Reduced risk of ischaemic stroke independently associated with high fruit and vegetable consumption. Risk estimates were non-significant for PFV juice
Joshiyura et al. (1999)	Nurses Health Study, $n=75,596$ women, 34–59 years old with 14 years follow-up; Health Professionals Study, $n=38,683$ men 40–75 years old with 8 years follow-up	Prospective cohort study, 14 year follow-up yielding $n=570$ cases ischaemic stroke	One additional daily serving of F&V associated with 6% lower risk of ischaemic stroke Citrus fruit juice, cruciferous vegetables, green leafy vegetables, citrus fruit contributed most to effect (relative risk, 0.75; 95% confidence interval, 0.61–0.93)
<b>Platelet aggregation (seven studies)</b>			
Dutta-Roy et al. (2001)	<i>In vitro</i> study	17 different fruit juices studied	Tomato juice was the most effective platelet inhibitor of the fruit juices tested
Lazarus and Garg (2004)	<i>In vitro</i> study	Tomato juice studied	The inhibition of platelet aggregation was found to be dose dependent
Lazarus et al. (2004)	$n=14$ men and 6 women, 43–82 years old with type 2 diabetes or impaired glucose tolerance	Double-blind, parallel-group study Consumption of clarified tomato juice or placebo tomato-flavoured beverage daily for 3 weeks	Platelet aggregation decreased following supplementation with tomato juice vs placebo Also significantly lower compared with baseline (area under curve, 13,767 [4658] vs 18730 [2783]; $P=0.001$ )

Table III (Continued)

Reference	Subjects	Study details	Outcomes
Freedman et al. (2001)	$n = 20$ healthy subjects (eight female), 20–45 years old, <i>in vivo</i> study	Subjects drank 7 ml/kg/day purple grape juice for 14 days. Platelets sampled and tested	Platelet aggregation reduced from $89.3 \pm 3.3\%$ to $50.5 \pm 3.7\%$ ( $p < 0.01$ )
Keevil et al. (2000)	$n = 10$ healthy subjects (five female), 26–58 years old	RCT. Subjects drank 5–7.5 ml/kg/day purple grape juice, orange juice or grapefruit juice for 7–10 days each  Platelet aggregation at baseline compared with results after consumption of each juice	Drinking purple grape juice reduced whole blood platelet aggregation response to 1 mg/l collagen by 77% (from $17.9 \pm 2.3$ to $4.0 \pm 6.8$ ohms, $p = 0.0002$ ) Orange juice and grapefruit juice had no effect on platelet aggregation
Folts (1998)	$n = 10$ healthy subjects, 21–55 years old	Comparison between consumption of red wine, white wine and purple grape juice (1 week apart)	A significant decrease in <i>ex vivo</i> whole blood platelet aggregation after consumption of red wine and purple grape juice, but not white wine
Pace-Asciak et al. (1996)	$n = 24$ healthy men, 26–45 years old	Each consumed the following beverages for 4 weeks: red wine, white wine, commercial grape juice, same grape juice enriched with <i>trans</i> -resveratrol	No significant changes were observed in platelet activity with either fruit juices
<b>Antioxidant capacity (20 studies)</b>			
Kiefer et al. (2004)	$n = 59$ healthy adults, 40–60 years old	14-week double-blind cross-over RCT. Subjects given: (a) fruit juice concentrate, (b) vegetable juice concentrate, (c) placebo Both (a) and (b) included B vitamins and folate to provide standardized carotene, vitamins C and E	Plasma levels of carotene, vitamin C, vitamin E, selenium and folate significantly increased  No significant changes for indicators of oxidative modification of cellular DNA
Aviram et al. (2004)	$n = 19$ subjects (five women) with atherosclerosis (carotid artery stenosis), 65–75 years old	Subjects randomized to receive 50 ml/day pomegranate juice ( $n = 10$ ) or placebo ( $n = 9$ ) for 1 year Five subjects continued on pomegranate juice for up to 3 years	In control group, common carotid intima-media thickness (IMT) increased by 9% at 1 year In active group, IMT reduction significantly reduced by up to 30%. Systolic blood pressure reduced after by 21% at 1 year Further consumption up to 3 years gave no additional benefit except that serum lipid peroxidation reduced by up to a further 16%

Table III (Continued)

Reference	Subjects	Study details	Outcomes
Samman et al. (2003)	<i>n</i> = 32 men (13 smokers, 19 non-smokers)	6-week double-blind cross-over RCT Supplementation by a mixed fruit and vegetable supplement produced from dehydrated juice concentrates versus placebo	Plasma antioxidant vitamins increased and plasma homocysteine was reduced Trend for higher FRAP after supplementation compared with placebo ( $1125.5 \pm 144.1$ vs. $1180.3 \pm 158.1$ $\mu\text{mol/l}$ ; $P < 0.065$ )
Johnston et al. (2003)	<i>n</i> = 11 subjects, mean age 29 years	3 $\times$ 3 randomized crossover design: (a) 2 week washout, (b) 8 fl oz orange juice, and (c) vitamin C supplement	Orange juice and vitamin C supplement significantly reduced a marker of lipid peroxidation in plasma
O'Byrne et al. (2002)	<i>n</i> = 36 healthy non-smokers	2-week RCT with subjects taking either: 10 ml Concord grape juice/kg/day, or 400 IU $\alpha$ -tocopherol	Concord grape juice increased serum antioxidant capacity and inhibited LDL oxidation to same extent as vitamin E Concord grape juice decreased native plasma protein oxidation significantly more than did vitamin E
Vinson et al. (2002)	<i>In vitro</i> study	Tangerine juice, grapefruit juice and orange juice were used as samples	Polyphenols in citrus juices were not able to bind with LDL and very LDL and inhibit oxidation
Maruyama et al. (2001)	<i>n</i> = 31 healthy students, Japan	28-day RCT with subjects taking either: 480 ml control drink, 160 ml tomato juice plus 320 ml control drink, or 480 ml tomato juice	Plasma lycopene and $\beta$ -carotene increased in groups 2 and 3. No significant differences in lag time before oxidation between groups. Lag time changes related to triglyceride alpha-tocopherol concentration in LDL
Chou et al. (2001)	<i>n</i> = 22 adults with coronary artery disease, mean 64 years old	56-day RCT with subjects taking purple grape juice as either: 8.0 ml/kg, twice daily, or 4.0 ml/kg, once daily. Vitamin E added after 28 days	Flow-mediated vasodilation of the brachial artery improved in both groups and there were similar effects on endothelial function. Adding vitamin E did not improve endothelial function further
Pederson et al. (2000)	<i>n</i> = 9 healthy women, 23–41 years old	After an overnight fast, subjects given 500 ml blueberry juice, cranberry juice or control (sucrose solution). Each subject consumed all 3 drinks with a 1 week washout	Plasma antioxidant capacity increased when cranberry juice was taken

Table III (Continued)

Reference	Subjects	Study details	Outcomes
Pearson et al. (1999)	<i>In vitro</i> study	Six commercial apple juices studied	Fresh apple juice inhibited LDL oxidation. There was no significant correlation between antioxidant activity and phenolic concentration or any specific class of phenolics
Smith et al. (1999)	<i>n</i> = 20 subjects >60 years old	80-day RCT with supplements of fruit extracts and vegetable extracts given twice daily	Significant reduction in DNA damage found in peripheral lymphocytes
Stein et al. (1999)	<i>n</i> = 15 adults with coronary artery disease	All subjects consumed 7.7 ml/kg/day purple grape juice for 14 days	Significant improvement in flow-mediated vasodilation with purple grape juice. LDL cholesterol susceptibility to oxidation decreased
Frankel et al. (1998)	<i>In vitro</i> study	Antioxidant capacity of commercial grape juices assessed by looking at human LDL oxidation	Grape juices inhibited LDL oxidation from 62% to 75%. Adding vitamin C had no significant effect on antioxidant capacity of the grape juices
Wilson et al. (1998)	<i>In vitro</i> study	Antioxidant capacity of cranberry juice assessed by looking at human LDL oxidation	Cranberry juice extracts inhibited the oxidative modification of LDL particles
Miyagi et al. (1997)	<i>n</i> = 20 healthy subjects (12 women), 20–53 years old, <i>in vitro</i> and <i>in vivo</i> study	RCT, subjects consumed either red wine, white wine, beer or grape juice. Total phenolic compounds and flavonoids similar in red wine and grape juice	<i>In vitro</i> antioxidant effect on LDL of grape juice closely associated with an abundance of flavonoids. <i>In vivo</i> antioxidant activity was not demonstrated in subjects ingesting grape juice
Day et al. (1997)	<i>n</i> = 7 subjects	Subjects consumed 125 ml red grape juice concentrate daily for 7 days	Total antioxidant capacity was 50 $\mu$ mol/l higher after grape juice compared with baseline ( <i>p</i> < 0.05). There was also reduced susceptibility of LDL to oxidation
Wise et al. (1996)	<i>n</i> = 15 healthy subjects, 18–53 years old	Subjects given dehydrated fruit and vegetable juice extracts for 28 days	Serum lipid peroxides decreased fourfold after 7 days and remained significantly lower at 28 days compared with baseline
Abu-Amsha et al. (1996)	<i>In vitro</i> study	Purple grape juice, red wine, white wine and beer studied	Higher polyphenolic content associated with a greater antioxidant effect on LDL

Table III (Continued)

Reference	Subjects	Study details	Outcomes
Lanningham-Foster et al. (1995)	<i>In vitro</i> study	Grape juice studied	Oxidative changes to LDL prevented by exposure to grape juice
Abbey et al. (1995)	<i>n</i> = 15 normolipidaemic male smokers	Subjects consumed a vitamin-free drink (fruit flavoured mineral water) for 3 weeks, then for further 3 weeks were given 250 ml orange juice and 300 ml carrot juice. Diet rich in polyunsaturated fatty acids followed throughout study	Slightly improved protection against LDL oxidation when fruit juice consumed for 3 weeks
<b>Serum lipoprotein levels (five studies)</b>			
Gorinstein et al. (2004a, 2004b)	<i>n</i> = 72 subjects with hypercholesterolemia, 43–71 years old	30-day RCT with subjects taking: 100 ml or 200 ml fresh ‘Sweetie’ juice, vs. no drink control	Total and LDL cholesterol significantly reduced in both ‘Sweetie’ juice groups vs control No significant change in serum albumin. Serum antioxidant capacities in 200 ml group significantly increased compared with control
Collins et al. (2004)	<i>n</i> = 10 healthy subjects (five women), mean age 50 years old; five moderately hypercholesterolaemic	Crossover study using low lycopene diet (control treatment) versus diet supplemented with watermelon or tomato juice, each containing 20 mg lycopene	Lycopene-containing foods did not affect plasma lipid concentrations or antioxidant biomarkers
Takai et al. (2003)	<i>n</i> = 77 subjects with mild to moderate hypercholesterolaemia	9-week double-blind RCT with subjects given beverages containing either broccoli or cabbage juice. Control group given placebo drink without the vegetable extracts	Serum LDL-cholesterol significantly reduced ( <i>p</i> < 0.05) in broccoli and cabbage supplemented group when baseline $\geq 140$ mg/dl Average reduction at 9 weeks was 8.5%
Suido et al. (2002)	<i>n</i> = 45 subjects with hypercholesterolemia, 22–59 years old	Two studies of a test beverage (blend of green vegetables and fruits): study 1, <i>n</i> 31, 160 g/day for 3 weeks; study 2, <i>n</i> = 14, 160 g/day for 12 weeks	Study 1: total and LDL cholesterol significantly decreased. Levels returned to baseline at 9 weeks after cessation of the beverage Study 2: Significant reductions in total and LDL cholesterol

Table III (Continued)

Reference	Subjects	Study details	Outcomes
Kurowska et al. (2000)	<i>n</i> = 25 healthy subjects (nine female) with elevated plasma total and LDL-cholesterol and normal plasma triacylglycerol concentrations	Cross-over study with subjects including 250 ml, 500 ml or 750 ml orange juice sequentially into their diets for 4 weeks per volume	Consumption of 750 ml orange juice only increased HDL cholesterol by 21% ( <i>p</i> < 0.001); increased triacylglycerol by 30%, decreased LDL-HDL ratio by 16% ( <i>p</i> < 0.005). No effect on homocysteine
<b>Plasma homocysteine levels (one study)</b>			
Panunzio et al. (2003)	<i>n</i> = 26 healthy subjects (14 women), 20–56 years old	4-week intervention trial of 2 capsules/day powdered fruit extract + vegetable extract. Subjects acted as own controls	Plasma tHcy decreased by $4.73 \pm 1.153$ $\mu\text{mol/l}$ with daily intake of extract ( <i>p</i> < 0.001)

RCT, randomized controlled trial; FFQ, food frequency questionnaire; FRAP, ferric reducing ability of plasma; HDL, high-density lipoprotein.

*Antioxidant capacity*

Twenty studies were included that examined the antioxidant capacity of PFV juices. One study that supplemented renal transplant patients with tomato juice (Sutherland et al. 1999) was excluded due to the special nature of the subject group.

Six *in vitro* studies were identified plus one study with both *in vitro* and *in vivo* components. Four studies examined the effects of purple grape juice, all reporting that the juice inhibited LDL oxidation and demonstrated an antioxidant effect (Lanningham-Foster et al. 1995; Abu-Amsha et al. 1996; Miyagi et al. 1997; Frankel et al. 1998). Studies on cranberry juice (Wilson et al. 1998) and apple juice (Pearson et al. 1999) also found inhibition of LDL oxidation. The apple juice result is counter-intuitive given work showing that antioxidants in commercial apple juice are typically removed along with the pulp during processing (van der Sluis et al. 2002). However, these authors also demonstrated that 55% of the total antioxidant activity in apple juice remained unaccounted for once known antioxidants were identified. Similar findings were reported for orange juice and blackcurrant juice, where 5% and 24%, respectively, of antioxidant potential remained unaccounted for (Miller and Rice-Evans 1997).

Support for the role of polyphenols, rather than vitamin C, as the major antioxidants in PFV juices comes from a number of studies. Vinson et al. (2002) reported that citrus juices (i.e. tangerine, grapefruit and orange) failed to protect LDL and very LDL from oxidation, which concurs with Hung et al. (2004) who found no association between CVD risk reduction and citrus fruit intake. Frankel et al. (1998) reported that vitamin C naturally present in grape juice contributed minimally to its overall antioxidant status, while Lugasi and Hovari (2003) noted that the polyphenol content of juices correlated strongly with plasma antioxidant status ( $p < 0.0001$ ).

Fourteen studies used *in vivo* methods to examine the antioxidant capacity of PFV juices. A broad range of PFV juices was used, yielding similar results in the majority of studies as detailed in Table III. Consumption of PFV juices, such as carrot, cranberry, pomegranate, tomato and orange, tended to increase plasma levels of antioxidant vitamins (Wise et al. 1996; Smith et al. 1999; Samman et al. 2003; Kiefer et al. 2004). A number of these studies also reported enhanced antioxidant activity (e.g. plasma ferric reducing/antioxidant power), DNA damage in peripheral lymphocytes and serum lipid peroxides. However, there were limited studies on each type of juice and sample sizes were fairly low.

The largest body of work related to grape juice, which had five studies. Four of these found similar results to those reported for other types of juices. In the two studies using subjects with CVD (Stein et al. 1999; Chou et al. 2001), grape juice consumption improved flow-mediated vasodilation. As before, sample sizes were fairly low and the durations were no greater than 28 days.

*Serum lipoprotein levels*

Five studies were located that looked at the effects of PFV juices on serum lipoprotein levels. Juices studied included 'sweetie juice' (a citrus fruit–pummelo–grapefruit hybrid; Gorinstein et al. 2004a,b), watermelon or tomato juice (Collins et al. 2004), vegetable juice (Takai et al. 2003), blend of vegetable and fruit juices (Suido et al. 2002) and orange juice (Kurowska et al. 2000).

Four studies used subjects with hypercholesterolaemia, finding that most PFV juices either reduced concentrations of LDL cholesterol or increased high-density

lipoprotein cholesterol (Kurowska et al. 2000; Suido et al. 2002; Takai et al. 2003; Gorinstein et al. 2004a,b). Tomato and watermelon juices did not affect plasma lipid concentrations or antioxidant biomarkers (Collins et al. 2004), although the subjects used were normocholesterolaemic

#### *Plasma homocysteine levels*

Total homocysteine (tHcy) is considered to be predictive of all-cause mortality as it may be directly involved in the process of oxidative damage (Malinow 2001). Only one study focused on plasma tHcy levels, finding reductions in healthy subjects after 4 weeks of supplementation with powdered PFV juice extract (Panunzio et al. 2003). Two studies mentioned previously (Samman et al. 2003; Keifer et al. 2004) were also taken into account as they included analysis of tHcy. These studies also found a positive effect of PFV juices on tHcy and serum folate concentrations (Samman et al. 2003; Kiefer et al. 2004). Declines in plasma tHcy have been achieved with a broad range of mean folate intakes; 200 µg/day from PFV juices (Panunzio et al. 2003) up to 560 µg/day from whole F&V (Brouwer et al. 1999), which is more than adults would normally consume from these sources.

In concluding this section, it appears that PFV juices impact favourably on a number of CVD risk factors, particularly platelet aggregation, LDL oxidation and LDL concentrations (in those with hypercholesterolaemia). Some PFV juices (e.g. tomato and purple grape juice) performed better than others. It would be useful to test these models further in longer-term human intervention trials.

## **Discussion**

To return to the two questions posed by this review, the available body of evidence fails to support the commonly-held view that PFV juices are somehow inferior to whole F&V in relation to chronic disease risk reduction. This is particularly the case for colorectal cancer, where consumption of insoluble, rather than soluble, fibre seemed to be associated with risk reduction. Epidemiology is a rather blunt tool and cannot be used on its own to deduce the separate effects of dietary components. The epidemiological data sourced for this review suggested at least similar associations between chronic disease risk and PFV juices or whole F&V. Clinical data, on the other hand, appeared to give more weight to antioxidants and phenolic compounds, rather than soluble fibre, for cancer and CVD risk reduction.

Addressing the second question, it was clear that the quality and clarity of evidence differed for cancer and CVD (for a summary see Table IV). The multi-factorial nature of cancer, combined with the time lag between early development and diagnosis, makes it problematic to study. While *in vitro* studies showed that PFV juices demonstrated antioxidant capabilities and reduced lymphocyte DNA damage, data from human trials were contradictory. It could be that the relative importance of dietary factors differs depending on the cancer site (e.g. fruits, vegetables and their juices appeared to have little effect on breast cancer risk). Thus, PFV juices may be protective in the development of some cancers, but not others (Steinmetz and Potter 1996). More studies are needed to investigate this point further.

The evidence for CVD is clearer, with PFV juices impacting on many areas of risk. Initially, antioxidant vitamins were thought to explain the majority of health effects

Table IV. Overview of results for the potential impact of pure fruit and vegetable juices on cancer and cardiovascular disease

Condition	Strength of evidence	Volume of evidence
Cancer	Strong evidence that PFV juice unrelated to breast cancer risk	Three references
	Weak association between PFV juice and an increased risk of renal cell carcinoma, but no convincing mechanism	Two references
	Insufficient number of human studies in other areas to make any meaningful comment on cancer risk or prevention	Three references
	Strong evidence that PFV juices significantly decrease lymphocyte damage	
Ischaemic stroke	Weak evidence of a positive association between PFV juice consumption and blood pressure reduction	Three references
Platelet aggregation	Moderate evidence from <i>in vitro</i> studies and human trials that tomato juice and purple grape juice have anti-platelet effects	Six references
Antioxidant capacity	Strong evidence from <i>in vitro</i> studies suggesting an antioxidant effect particularly related to polyphenol content	Six references
	Strong evidence from human trials and <i>in vivo</i> studies suggesting prevention of LDL oxidation in healthy subjects	12 references
	Weak evidence of improved endothelial-dependent vasodilation in subjects with coronary artery disease	Two references
Serum lipoprotein levels	Moderate evidence that PFV juices can reduce plasma LDL levels in subjects with hypercholesterolaemia	Four references
Plasma homocysteine levels	Weak evidence suggestive of beneficial effects on plasma homocysteine levels	Three references

related to consumption of PFV juices. However, other candidates have come to the fore; chiefly polyphenols, which appear to act independently from ascorbic acid and tocopherols (Lugasi and Hovari 2003). This is demonstrated in the *in vitro* studies showing similarities in antioxidant activity for a number of juices yet differences in LDL and very LDL oxidation (see Table III). Frankel et al. (1998) also found that vitamin C from purple grape juice had no significant effect on its antioxidant capacity, suggesting that polyphenols or other components were the active constituents of this juice. Both purple grape juice and red wine contain polyphenols exhibited significant anti-platelet characteristics (Folts 1998). In comparison, similar effects were not seen for orange juice, grapefruit juice or white wine (Folts 1998; Keevil et al. 2000). Other constituents of PFV juices that could benefit CVD risk include potassium and folate (Strazzullo et al. 2004).

Just as the steps leading up to atherosclerosis are complex, the mechanisms by which PFV juices might maintain heart health are varied. Apart from the antioxidant effect on lipoproteins, it would seem that polyphenols significantly improve endothelial function and flow-mediated vasodilation in subjects with coronary artery disease (Stein et al. 1999; Chou et al. 2001). It is also possible that the hypotensive

effects of grape juice consumption may be explained by the inhibitory effect of angiotensin-converting enzyme activity through increased availability of nitrogen oxide (Park et al., 2004).

A reasonable conclusion from the available evidence is that PFV juices *do* appear to possess the necessary nutrients for CVD risk reduction. For cancer risk, the weight of evidence for PFV juices seems similar to that for whole F&V since it is not clear that soluble fibre plays a key protective role. An exception is pectin, for which there is some *in vitro* evidence of benefit, but this can be present in both whole and juiced F&V. The low fibre content of PFV juices may, in fact, offer one advantage over whole F&V. McEligot et al. (1999) reported that women who drank vegetable juices daily had higher serum concentrations of lutein and  $\alpha$ -carotene compared with women who ate a similar amount of whole vegetables. The authors suggested that the juicing process reduced particle size and increased bioavailability of carotenoids.

However, before current dietary policy is criticized, one needs to examine other aspects of fruit juices that could attract concern; namely, potential links with obesity, micronutrient dilution and dental caries/erosion. There are no studies examining the effects of vegetable juices on these variables.

Health professionals traditionally recommend that children limit their intake of fruit juices to prevent the development of obesity. Certainly fruit juices can be consumed more quickly, and in larger quantities, than fresh fruit, thus having the potential to boost energy intakes. However, studies that have attempted to link fruit juices with obesity have found conflicting effects (Alexy et al. 1999; Skinner et al. 1999; Skinner and Carruth 2001; Newby et al. 2004) and none supported the restriction of fruit juices. Indeed, Skinner and Carruth (2001) noted an inverse relationship between fruit juices and intakes of less nutritious beverages in children, and concluded that fruit juices should be encouraged.

With respect to micronutrient dilution, Marshall et al. (2005) looked at the displacement of milk by fruit juices in children aged 1–5 years. While fruit juice consumption was strongly associated with vitamin C intake, it was inversely associated with nutrients typically found in milk in 2 year olds, which suggests some displacement. Moderation is key, as endorsed by the American Academy of Pediatrics (2001) stating that ‘100% fruit juice or reconstituted juice can be a healthy part of the diet when consumed as part of a well-balanced diet’ and that ‘a variety of fruit juices, provided in appropriate amounts for a child’s age, are not likely to cause any significant clinical symptoms’.

Turning to dental health, all fermentable carbohydrates theoretically contribute to the development of caries (Food and Agricultural Organisation 1998) so fruit and fruit juices could play a role in caries development. Indeed, it has been suggested that the presence of free sugars in fruit juices make them more cariogenic than fruit (Department of Health 1989). This was investigated by Hussein et al. (1996) using standard measurements of plaque pH. No differences were found between the amounts of acid generated by whole, homogenized or juiced fruits, suggesting that they were equally cariogenic. The liquid nature of fruit juice may mean that it remains in contact with the teeth for a short period of time compared with solid foods (Tahmassebi and Duggal 1997). The British Dental Association has stated that ‘the frequency and amount of consumption of sugars in drinks and foods are the most important risk factors [in the development of dental caries]’ (Levine and Stillman-Lowe 2004). In contrast, novel research in animals has suggested that apple

polyphenols added to animal feeds inhibited caries development due to their antibacterial nature (Cordeiro et al. 2000). The effects were unrelated to the fibrous components, as these were removed. It could be an interesting area to explore in humans.

Due to the acidic nature of fruit juice, it has the potential to cause erosion. Recommendations include restricting it to meal times (Levine and Stillman-Lowe 2004), using a straw (Tahmassebi and Duggal 1997) and avoiding prolonged contact with the teeth (American Academy of Pediatrics 2001).

## Conclusion

When considering cancer and coronary heart disease prevention, there is no evidence that pure fruit and vegetable juices are less beneficial than whole fruit and vegetables. Thus, policies that maintain pure fruit and vegetable juices are somehow nutritionally inferior are unjustified and should be re-examined. Concerns that pure fruit and vegetable juices may impact negatively on body weight, micronutrient dilution and dental health are not borne out in the literature.

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**Appendix 1: Search criteria**

All human studies published from January 1995 to March 2005 including epidemiological, *in vitro*, *in vivo* and intervention

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 Search terms
 

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Cancer	'fruit and vegetable juice and cancer' 'fruit and vegetables and cancer'
Coronary vascular disease	'fruit and vegetable juice and stroke' 'fruit and vegetable juice and high blood pressure' 'fruit and vegetable juice and hypertension' 'fruit and vegetable juice and coronary heart disease' 'fruit and vegetables and stroke' 'fruit and vegetables and high blood pressure' 'fruit and vegetables and hypertension' 'fruit and vegetables and coronary heart disease'

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**Appendix 2: Levels of evidence adapted from Scottish Intercollegiate Guidelines Network grading system**

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- 1 Meta-analyses, randomized controlled trials, systematic reviews of randomized controlled trials
  - 2 Systematic reviews of case control or cohort studies, and case-control or cohort studies with a moderate to high probability that the relationship is causal
  - 3 Non-randomized controlled trials interventions, epidemiology, *in vitro* studies, *in vivo* studies and case reports
  - 4 Expert opinion
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