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Review Article

Apple intake and cancer risk: a systematic review and meta-analysis of observational studies

Roberto Fabiani[1,*], Liliana Minelli[2] and Patrizia Rosignoli[1]
[1]Department of Chemistry, Biology and Biotechnology, University of Perugia, Via del Giochetto, 06126 Perugia, Italy: [2]Department of Experimental Medicine, University of Perugia, Perugia, Italy

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Abstract

Objective: Conflicting results on the association between fruit consumption and cancer risk have been reported. Little is known about the cancer preventive effects of different fruit types. The present meta-analysis investigates whether an association exists between apple intake and cancer risk.

Design: Relevant observational studies were identified by literature search (PubMed, Web of Science and Embase). A random-effect model was used to estimate the cancer risk in different anatomical sites. Between-study heterogeneity and publication bias were assessed using adequate statistical tests.

Results: Twenty case–control (three on lung, five on colorectal, five on breast, two on oesophageal, three on oral cavity, two on prostate and one each on pancreas, bladder, larynx, ovary, kidney and brain cancer) and twenty-one cohort (seven on lung, two on colorectal, three on breast and one each on oesophageal, pancreas, bladder, kidney, endometrial, head–neck, urothelial and stomach cancer) studies met the inclusion criteria. Comparing the highest *v.* lowest level of apple consumption, the reduction of lung cancer risk was statistically highly significant in both case–control (OR = 0·75; 95 % CI 0·63, 0·88; $P = 0·001$, $I^2 = 0\,\%$) and cohort studies (relative risk = 0·89; 95 % CI 0·84, 0·94; $P < 0·001$, $I^2 = 53\,\%$). Instead, in the case of colorectal (OR = 0·66; 95 % CI 0·54, 0·81; $P < 0·001$, $I^2 = 55\,\%$), breast (OR = 0·79; 95 % CI 0·73, 0·87; $P < 0·001$, $I^2 = 1\,\%$) and overall digestive tract (OR = 0·50; 95 % CI 0·36, 0·69; $P < 0·001$, $I^2 = 90\,\%$) cancers a significant preventive effect of apples was found only in case–control studies while prospective studies indicated no effect. No evidence of publication bias could be detected for colorectal, oral cavity, oesophageal and breast cancer. However, some confounding effects may be present and related to the consumption of other fruit which have not been considered as adjusting factors.

Conclusions: The present meta-analysis indicates that consumption of apples is associated with a reduced risk of cancer in different anatomical sites.

Keywords
Cancer prevention
Apple intake
Dietary
Epidemiology
Meta-analysis

Cancer is a chronic degenerative disease causing major morbidity and mortality in Western countries. It has been estimated that in the year 2012, 14·1 million new cancer cases were diagnosed and 8·2 million cancer deaths were established[1]. The overall age-standardized cancer incidence rates vary three- to fivefold across different regions of the world[2]. These variations may be related to different modifiable risk and preventive factors among which diet may play a central role. It has been estimated that about one-third of all cancer could be avoidable by changes in eating habits[3].

Foods of plant origin have received particular interest over the years as potential cancer-preventive components of a healthy diet. Fruit and vegetables contain a myriad of bioactive phytochemicals that, through various molecular mechanisms, show chemopreventive properties in both *in vitro* and *in vivo* models of carcinogenesis[4]. However, from an epidemiological point of view, while early data from case–control studies suggested a clear preventive role for fruit and vegetables on cancer in different sites, recent large prospective studies have questioned this conclusion[5]. Indeed, while an expert panel report from the World Cancer Research Fund/American Institute for Cancer Research published in 1997 stated that there was 'convincing' evidence that a high intake of fruit and/or

*Corresponding author: Email roberto.fabiani@unipg.it

vegetables prevents cancers, an updated report published 10 years later downgraded the evidence to either 'probable' or 'limited-suggestive'[6].

Because of the peculiar chemical composition and the potential molecular mechanisms involved, it is possible that some types of fruit/vegetable may be much more strongly associated with cancer risk than others. This may be hidden in epidemiological studies examining the association of cancer risk with total fruit/vegetable intake. In this respect, our interest was attracted by apples considering that they are the most consumed fruit in European countries and they are a rich source of bioactive phytochemicals (phenols and flavonoids) possessing strong chemopreventive and antioxidant activities[7]. We therefore conducted a systematic review of the literature on the relationship between apple intake and cancer risk, and for the first time undertook a meta-analysis to provide quantitative estimates of the association.

Materials and methods

Literature search strategy

We carried out a comprehensive literature search, without restrictions, up to December 2015 through PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (http://wokinfo.com/) and Embase (http://www.embase.com) to identify all original articles on the association between apple intake and cancer risk using the following search keywords: (apple OR apples OR *Rosaceae* OR *Malus domestica*) AND (cancer OR neoplastic disease OR neoplasm). Furthermore, the reference lists of included articles and recent relevant reviews were manually examined to identify additional relevant publications. The standard procedures for conducting and reporting meta-analysis according to the guidelines from the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group were followed[8].

Selection criteria

Potential identified articles were included if they met the following criteria: (i) used a case–control or prospective study design; (ii) evaluated the association between apple intake and cancer risk; and (iii) presented OR, relative risk (RR) or hazard ratio (HR) estimates with 95 % CI. When there were several publications from the same study, the publication with the largest number of cases was selected. Although useful to have background information, reviews and meta-analysis were excluded.

Data abstraction and quality assessment

For each potential study included, two investigators independently carried out the selection evaluation, data abstraction and quality assessment; disagreements between evaluators concerning the selected studies were resolved by discussion or in consultation with a third author. From the selected studies we extracted the following data: the first author's last name, year of publication, study region and design, tumour site, sample size (number of cases and controls; cohort size and incident cases), age, duration of follow-up for cohort studies, dietary assessment method, apple intake and OR/RR/HR estimates with 95 % CI for the highest *v.* lowest category of apple intake. When multiple estimates were reported in the article, we abstracted those that adjusted for the most confounding factors. If separate risk estimates for males and females were available in one study, we treated them as two separate studies.

The study quality was assessed by a nine-star system based on the Newcastle–Ottawa Scale method[9]. The full score was 9 and a total score ≥7 was used to indicate a high-quality study. To avoid selection bias, no study was excluded because of these quality criteria.

Statistical analysis

For the overall estimation, the HR and RR were taken to be approximations to OR, and the meta-analysis was done as if all types of ratio were OR. The combined risk estimates were calculated using the random-effects model.

The χ^2-based Cochran's Q statistic and the I^2 statistic were used to evaluate heterogeneity in results across studies. For the Q statistic, a P value <0·1 was considered to be representative of statistically significant heterogeneity. The I^2 statistic yields results ranging from 0 to 100 % ($I^2 = 0$–25 %, absent; $I^2 = 25$–50 %, low; $I^2 = 50$–75 %, moderate; and $I^2 = 75$–100 %, high heterogeneity).

Analysis of publication bias was carried out by both Egger's linear regression test and Begg's rank correlation test. Both methods test for funnel plot asymmetry, the former being based on the rank correlation between the effect estimates and their sampling variances, and the latter on a linear regression of a standard normal deviate on its precision. If a potential bias was detected, we further conducted a sensitivity analysis to assess the robustness of combined effect estimates and the possible influence of the bias and to have the bias corrected. A sensitivity analysis was conducted to investigate the influence of a single study on the risk estimate by omitting each study in turn. Funnel plots were considered asymmetric if the intercept of Egger's regression line deviated from zero with a P value of <0·05. The ProMeta Version 2·0 statistical program (Internovi) was used for the analysis. All reported P values are from two-sided statistical tests and differences with $P \leq 0{\cdot}05$ were considered significant.

Results

Literature search

As shown in Fig. 1, 2923 articles were obtained by searching the three different databases (PubMed, Web of Science and Embase). After excluding 997 duplicates, 1926 records were identified for title and abstract revision. Of

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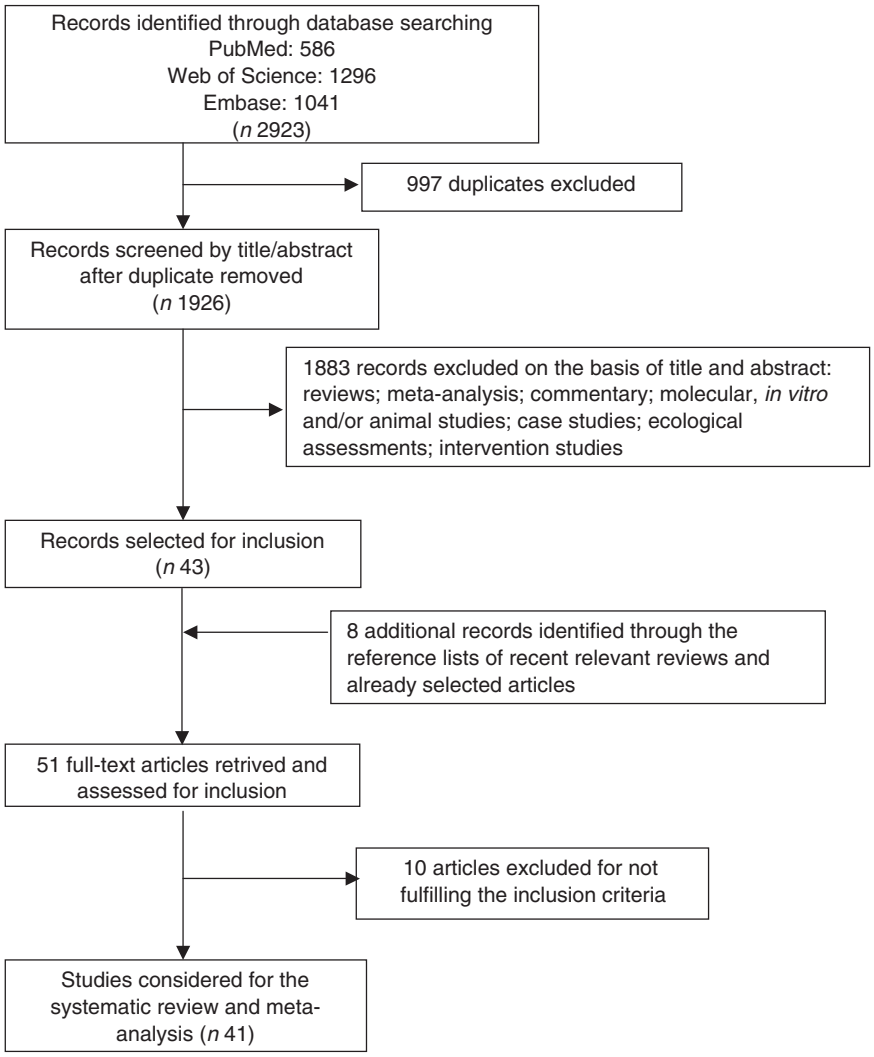

Fig. 1 Flowchart of the selection process for inclusion of studies in the meta-analysis

the 1926 articles screened, 1883 were excluded because they were not observational studies, leaving forty-three articles for full-text revision. Hand searching of reference lists of both selected articles and recent relevant reviews led to the identification of eight additional items. Ten papers were subsequently excluded because they did not met the inclusion criteria as follows: two studies did not report the amount of apple intake; three articles reported the same data of a previous publication; two publications (lowest case numbers) were from the same study; one study did not report the risk estimate and another did not report the CI; and one evaluated the cancer risk in association with apple juice and cider. Therefore, at the end of the selection process, forty-one studies met the inclusion criteria and were included in the systematic review and meta-analysis[10–50].

Study characteristics and quality assessment

Of the forty-one selected papers, twenty were case–control studies[10–29], seventeen were cohort studies[30–46] and four were pooled analyses of cohort studies[47–50]. General characteristics of case–control and cohort studies are shown in Tables 1 and 2, respectively.

Case–control studies were published between 1994 and 2014; three were conducted in Italy[13,19,22], two each in Iran[10,15], China[12,23] and Australia[14,29], and one each in Poland[16], Spain[11], Czech Republic[17], Brazil[18], UK[20], India[24], Hawaii[25], Mexico[26], Sweden[27] and Uruguay[28]. One was a multinational study conducted in nine countries worldwide (Italy, Spain, Poland, Northern Ireland, India, Cuba, Canada, Australia and Sudan)[21]. Three case–control studies were on lung cancer (2049 cases and 4044 controls), five on colorectal cancer (3319 cases and 10 158 controls), five on breast cancer (7682 cases and 11 880 controls), two on oesophageal cancer (447 cases and 6725 controls), three on oral cavity cancer (2859 cases and 8943 controls), two on prostate cancer (1344 cases and; 6729 controls) and one each on pancreas, bladder, larynx, ovary, kidney and brain (glioma) cancer.

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Table 1 Characteristics of case–control studies on apple consumption in association with various types of cancer included in the systematic review

First author, year, reference, location	No. of cases/controls (age)	Dietary assessment	Apple intake comparisons	OR	95 % CI	Confounding factors adjusted for
Lung cancer *n* 3						
Tarrazzo-Antelo (2014)[11], Spain	371 (median 69 years)/ 496 (median 63 years)	FFQ	Apples: ≥once/d (T3; high) *v.* <once/ week (T1; low)	0·75	0·49, 1·15	Age, sex, smoking
Kubik (2008)[17], Czech Republic	509 males, 587 females/ 788 males, 2178 females (25–89 years)	FFQ 9 food items	Apples: Daily or several times per week (high) *v.* never (low)	Females: Current smokers 0·77 Never smokers 0·93 Males: Current smokers 0·77 Never smokers 0·54	0·56, 1·04 0·61, 1·41 0·54, 1·10 0·29, 1·09	Age, residence, education, smoking
Le Marchand (2000)[25], Hawaii, USA	375 males (mean 65·5 years), 207 females (mean 66·0 years)/ 375 males (mean 65·4 years), 207 females (mean 65·6 years)	Validated FFQ 242 food items	Apples, g/d: >49·7 (Q4; high) *v.* <2·3 (Q1; low)	0·6	0·4, 1·0	Age, sex, ethnicity, smoking, β-carotene, saturated fat
Colorectal cancer (*n* 5)						
Annema (2011)[14], Western Australia	918 (40–79, mean 64·9 (SD 8·9) years)/ 1021 (mean 64·6 (SD 9·4) years)	FFQ 74 food items	Apples, servings/d: ≥0·50 (Q4; high) *v.* <0·07 (Q1; low)	0·74	0·56, 0·99	Age, sex, BMI at age 20 years, EI, multivitamin, alcohol, PA, smoking, diabetes, SES
Jedrychowski (2010)[16], Poland	592/765 N/A	EPIC–FFQ 148 food items	Apples, servings/d: >1·5 (Q5; high) *v.* <0·18 (Q1; low)	0·53	0·35, 0·79	Age, sex, place of residency, marital status, smoking, total EI, intake of vegetables, intake of fruits
Theodoratou (2007)[20], UK	1456 (mean 63·9 (SD 9·6) years)/ 1456 (mean 64·7 (SD 9·5) years)	Validated FFQ 150 food items	Apples: Q4 (high) *v.* Q1 (low)	0·96	0·62, 1·50	Age, sex, residence area, family history of CRC, total EI, fibre, alcohol, NSAID, smoking, BMI, PA
Gallus (2005)[22], Italy	193/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·70	0·62, 0·79	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake
Deneo-Pellegrini (1996)[28], Uruguay	160 (mean 64·7 years)/ 287 (mean 65·3 years)	FFQ 50 food items	Apples: T3 (high) *v.* T1 (low)	0·40	0·25, 0·66	Age, sex, residence, BMI, total EI, alcohol
Breast cancer (*n* 5)						
Bao (2012)[12], China	3423/3464 (25–70 years)	Validated FFQ 76 food items	*Rosaceae* (apples, pears and peaches), g/d: ≥91·13 (Q5; high) *v.* <12·51 (Q1; low)	0·84	0·71, 0·98	Age, education, family history of breast cancer, history of breast fibro-adenoma, exercise, BMI, age at menarche, menopausal status, total meat, total fruit, total vegetables
Di Pietro (2007)[18], Brazil	33/33 (30–70 years)	FFQ 91 food items	Apples: weekly (high) *v.* never/rarely (low)	0·30	0·09, 0·94	Family income
Gallus (2005)[22], Italy	2569/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·76	0·67, 0·85	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake

Table 1 *Continued*

First author, year, reference, location	No. of cases/controls (age)	Dietary assessment	Apple intake comparisons	OR	95 % CI	Confounding factors adjusted for
Malin (2003)[23], China	1459 (47·8 (SD 8·0) years)/ 1556 (47·2 (SD 8·8) years)	Validated FFQ 76 food items	Apples, g/d: >57·0 (Q5; high) *v.* <3·2 (Q1; low)	0·86	0·66, 1·11	Age, education, family history of breast cancer and fibro-adenoma, WHR, menarche age, PA, ever had live birth, age at first live birth, total EI
Torres-Sánchez (2000)[26], Mexico	198/198 (29–71 years)	Validated FFQ 95 food items	Apples, pieces/week: ≥1 (high) *v.* <1 (low)	0·83	0·54, 1·28	Age, total EI, age at menarche, number of children, age at first birth, lifetime lactation, family history of breast cancer
Oesophageal cancer (*n* 2)						
Hajizadeh (2011)[15], Iran	47 (40–75, mean 58 (SD 10·1) years)/ 96 (mean 58 (SD 10·4) years)	Validated FFQ 168 food items	Apples: T3 (high) *v.* T1 (low)	0·33	0·04, 1·10	Age, sex, education, smoking, BMI, symptomatic gastro-oesophageal reflux, total EI
Gallus (2005)[22], Italy	304/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·78	0·56, 1·09	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake
Pancreatic cancer						
Rossi (2012)[13], Italy	326/652 (34–80, median 63 years)	Validated FFQ 78 food items	Apples and pears, portions/d: ≥3 (Q5; high) *v.* <0·5 (Q1; low)	0·35	0·15, 0·82	Age, sex, study centre, year of interview, education, history of diabetes, smoking, alcohol, non-alcohol EI
Bladder cancer						
Sacerdote (2007)[19], Italy	266/193 (40–75 years)	FFQ 22 food items	Apples: >median (high) *v.* ≤median (low)	0·63	0·39, 0·99	Age, smoking status and maximum number of cigarettes
Oral cavity cancer (*n* 3)						
Kreimer (2006)[21], nine countries (Italy, Spain, Poland, Northern Ireland, India, Cuba, Canada, Australia and Sudan)	1670/1732 N/A	FFQ 25 food items	Apples and pears: Q4 (high) *v.* Q1 (low)	0·4	0·3, 0·5	Age, sex, country, education, tobacco smoking, tobacco chewing, alcohol, BMI, total number of portions per week
Gallus (2005)[22], Italy	598/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·82	0·65, 1·05	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake
Rajkumar (2003)[24], Southern India	309 males (22–85, median 56 years), 282 females (18–87, median 58 years) 292 males (20–76, median 55 years), 290 females (18–80, median 52 years)	FFQ 21 food items	Apples or pears, servings/ week: ≥1 (T3; high) *v.* 0 (T1; low)	0·04	0·02, 0·08	Age, sex, centre, education, chewing, smoking, drinking habits

Table 1 *Continued*

First author, year, reference, location	No. of cases/controls (age)	Dietary assessment	Apple intake comparisons	OR	95 % CI	Confounding factors adjusted for
Larynx cancer						
Gallus (2005)[22], Italy	460/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·59	0·45, 0·78	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake
Ovarian cancer						
Gallus (2005)[22], Italy	1031/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·76	0·65, 0·90	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake
Prostate cancer						
Gallus (2005)[22], Italy	1294/6629 N/A	FFQ 78 food items	Apples, portions/d: ≥1 (high) *v.* <1 (low)	0·93	0·79, 1·10	Age, sex, study centre, education, BMI, smoking, alcohol, total EI, vegetable consumption, PA, other fruit intake
Askari (2014)[10], Iran	50 (40–78 years)/ 100 (43–71 years)	Validated FFQ 168 food items	Apple, g/d: >56·41 (T3; high) *v.* <7·59 (T1; low)	0·60	0·02, 1·03	Age, diabetes, smoking, total EI
Kidney cancer						
Lindblad (1997)[27], Sweden	379 males (mean 63·6 years) and females (mean 64·4 years)/ 350 males (mean 62·7 years) and females (63·4 years)	FFQ 63 food items	Apples, g/week: >656 (Q4; high) *v.* <105 (Q1; low)	0·65	0·43, 0·98	Age, sex, BMI, smoking, educational level
Brain cancer (glioma)						
Giles (1994)[29], Australia	243 males (mean 50·0 years), 166 females (mean 48·8 years)/ 243 males (mean 50·8 years), 166 females (mean 49·9 years)	FFQ 59 food items	Apples: Q4 (high) *v.* Q1 (low)	Males 2·04 Females 1·00	1·04, 4·00 0·25, 4·04	Age, alcohol, smoking

N/A, not available; EPIIC, European Prospective Investigation into Cancer and Nutrition; EI, energy intake; PA, physical activity; SES, socio-economic status; CRC, colorectal cancer; NSAID; non-steroidal anti-inflammatory drugs; WHR, waist-to-hip ratio.

Table 2 Characteristics of cohort studies on apple consumption in association with various types of cancer included in the systematic review

First author, year, reference, location	No. of subjects, (age), follow-up	Dietary assessment	Apple intake comparisons	HR/RR	95 % CI	Confounding factors adjusted for
Lung cancer (*n* 7)						
Büchner (2010)[32], ten European countries (EPIC)	478 535 cohort 1830 incident cases (25–70 years) Follow-up 8·7 years	Validated FFQ	Apples and pears (hard fruit): increments of 25 g/d	Full cohort 0·99 Current smokers 0·99	0·96–1·02 0·97, 1·01	Age, sex, vegetable consumption, smoking, EI, weight, height, alcohol, PA, school level
Wright (2008)[36], USA	472 081 cohort 6035 incident cases (50–71 years) Follow-up 8 years	Validated FFQ 124 food items	*Rosaceae**, servings/1000 kcal per d: Males 0·72 (Q5; high) *v.* 0·003 (Q1; low) Females 0·94 (Q5; high) *v.* 0·005 (Q1; low)	Males: Full cohort 0·82 Never smokers 0·75 Former smokers 0·81 Current smokers 0·76 Females: Full cohort 0·97 Never smokers 1·31 Former smokers 0·91 Current smokers 1·01	 0·73, 0·91 0·45, 1·26 0·70, 0·93 0·62, 0·94 0·85, 1·12 0·76, 2·26 0·73, 1·13 0·82, 1·24	Age, EI, race, education, BMI, smoking status, smoking dose, time since quitting smoking, alcohol intake, PA, family history of any cancer
Linseisen (2007)[38], ten European countries (EPIC)	478 590 cohort 1126 incident cases (608 males, 518 females) (25–70 years) Follow-up 6·4 years	Calibrated FFQ, 24 h diet recalls	Apples and pears, g/d: 115·0–2269·4 (Q5; high) *v.* 0–11·8 (Q1; low)	Full cohort 0·85 Never smokers 0·95 Former smokers 1·19 Current smokers 0·80	0·69, 1·05 0·41, 2·22 0·77, 1·83 0·62, 1·04	Age, weight and height, red meat, processed meat, alcohol, energy (fat and non-fat), PA, education, smoking
Knekt (2002)[42], Finland	5218 male cohort 169 incident cases (mean 39·3 (SD 15·8) years) Follow-up max. 30 years	FFQ >100 food items	Apples, g/d: >4·0 (Q4; high) *v.* 0·0 (Q1; low)	0·40	0·22, 0·74	Age, sex, geographic area, occupation, smoking, BMI
Arts (2001)[43], Netherlands	728 cohort, male 96 incident cases (65–84 years) Follow-up 10 years	Cross-check dietary history method	7·5 mg catechin intake increase from apples	0·67	0·38, 1·17	Age, other catechin sources, PA, total EI, alcohol, smoking, BMI, coffee, fibre, vitamin C, vitamin E, β-carotene
Feskanich (2000)[45], USA (NHS)	77 283 female cohort 519 incident cases (30–55 years) Follow-up 12 years	Validated FFQ 6 fruit/23 vegetable items	Apples and pears: increases of 1 serving/d	0·63	0·43, 0·91	Age, follow-up cycle, smoking status, EI, availability of diet data after baseline measure
Smith-Warner (2003)[48], USA–Canada–Europe Pooled analysis Seven studies	262 429 female cohort 137 336 male cohort 3138 incident cases Follow-up 6–16 years	Validated FFQ 6–26 fruit items	Apples, pears, servings/d: ≥0·5 (Q4; high) *v.* <0 (Q1; low)	0·80	0·68, 0·94	Education, BMI, alcohol intake, EI, smoking status
Colorectal cancer (*n* 2)						
Lin (2006)[39], USA (NHS and HPFS)	71 976 female cohort 498 incident cases (30–55 years) 35 425 male cohort 380 incident cases (40–75 years) Follow-up 10 years	Validated FFQ 131 food items	Apple: ≥2 servings/d (Q5; high) *v.* 0–2 servings/week (Q1; low)	NHS females 0·64 HPFS males 0·82	0·35, 1·17 0·51, 1·30	Age, BMI, PA, history of CRC, previous colorectal polyps, prior screening sigmoidoscopy or colonoscopy, smoking, multivitamin use, current aspirin use, alcohol, EI, red meat, total Ca, total folate, total fibre
Koushik (2007)[49], USA–Canada–Europe Pooled analysis Eleven studies	688 904 cohort (202 479 males, 486 425 females) 5489 incident cases (1651 males, 3838 females) Follow-up 8–21 years	Validated FFQ 4–21 fruit items	Apples, pears, applesauce, servings/d: ≥0·5 (Q4; high) *v.* <0 (Q1; low)	0·98	0·88, 1·10	Age, BMI, height, education, PA, family history of CRC, postmenopausal hormone use, OC use, use of NSAID, multivitamin use, smoking, red meat, total milk, alcohol, EI
Breast cancer (*n* 3)						
Boggs (2010)[30], USA	51 928 female cohort 1268 incident cases (21–69 years) Follow-up 12 years	Validated FFQ 85 food items	Apples: ≥3 servings/week (Q4; high) *v.* <1 serving/month (Q1; low)	1·02	0·83, 1·25	Age, EI, age at menarche, BMI at age 18 years, family history of breast cancer, education, geographic region, parity, age at first birth, OC use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking, alcohol, multivitamin use

Table 2 *Continued*

First author, year, reference, location	No. of subjects, (age), follow-up	Dietary assessment	Apple intake comparisons	HR/RR	95 % CI	Confounding factors adjusted for
Adebamowo (2005)[40], USA (NHS)	90 638 female cohort 710 incident cases (25–46 years) Follow-up 8 years	Validated FFQ 133–142 items	Apples: 1 servings/d (S6; high) *v.* <1 servings/month (S1; low)	1·16	0·77, 1·76	Age at menarche, parity, age at first birth, family history of breast cancer and benign breast disease, OC use, alcohol, BMI, EI, smoking, PA, menopausal status
Smith-Warner (2001)[47], USA–Canada–Europe Pooled analysis Seven studies	336 653 female cohort 7217 incident cases Follow-up 6–11 years	Validated FFQ 4–21 fruit items	Apple, pears: 100 g/d intake increment	0·97	0·93, 1·01	Age at menarche, interaction between parity and age at birth of first child, OC use, history of benign breast disease, menopausal status, postmenopausal hormone use, family history of breast cancer, smoking, education, BMI, height, alcohol, EI
Oesophageal cancer						
Freedman (2007)[37], USA	490 802 cohort (292 898 males, 197 904 females) 316 incident cases (103 ESCC, 213 EAC) (>50 years) Follow-up 5 years	Validated FFQ 124 food items	*Rosaceae*, servings/1000 kcal: 0·63 (T3; high) *v.* 0·06 (T1; low)	ESCC 0·34 EAC 0·99	0·18, 0·65 0·70, 1·39	Age, sex, education, BMI, alcohol, smoking, PA, total EI
Pancreatic cancer						
Koushik (2007)[50], USA–Canada–Europe–Australia Pooled analysis Fourteen studies	862 584 cohort 2185 incident cases	Validated FFQ 5–23 fruit items	Apples, pears, applesauce: 3 servings/week intake increment	0·98	0·94, 1·03	Age, smoking, alcohol, history of diabetes, BMI, height, EI
Bladder cancer						
Büchner (2009)[33], ten European countries (EPIC)	478 533 cohort 1015 incident cases (25–70 years) Follow-up 8·7 years	Validated FFQ	Apples and pears (hard fruit): increments of 2 5 g/d	0·90	0·82, 0·98	Age, sex, smoking, EI from fat and non-fat sources, vegetable consumption
Kidney cancer						
Rashidkhani (2005)[41], Sweden	61 000 female cohort 122 incident cases Follow-up 13·4 years	Validated FFQ Sixty-seven items	Apple, serving/d: ≥1 (T3; high) *v.* 0 (T1; low)	0·66	0·36, 1·18	Age, BMI
Endometrial cancer						
Kabat (2010)[31], USA	112 088 female cohort 1142 incident cases (50–71 years) Follow-up 8 years	Validated FFQ 124 food items	*Rosaceae*, servings/1000 kcal per d: ≥0·56 (Q5; high) *v.* <0·07 (Q1; low)	1·14	0·94, 1·39	Age, race/ethnicity, education, age at menarche, parity, hormone therapy, age at menopause, BMI, smoking, PA, total fat intake, EI
Head–neck cancer						
Freedman (2008)[35], USA	490 802 cohort 787 incident cases (50–71 years) Follow-up 4·5 years	Validated FFQ	*Rosaceae*, servings/1000 kcal per d: 0·6 (high) *v.* 0·1 (low)	0·60	0·49, 0·73	Age, sex, alcohol, BMI, smoking, education, total EI, usual activity throughout the day, PA
Urothelial cancer						
Zeegers (2001)[44], Netherlands	3123 cohort 619 incident cases (55–69 years) Follow-up 6·3 years	Validated FFQ 150 items	Apples and pears: increases of 25 g/d	0·97	0·91, 1·03	Age, sex, smoking, total fruit consumption, total vegetable consumption
Stomach cancer						
Botterweck (1998)[46], Netherlands	120 852 cohort 282 incident cases (55–69 years) Follow-up 6·3 years	Validated FFQ 150 items	Apples and pears, median intake, g/d: 232·0 (Q5; high) *v.* 0·0 (Q1; low)	0·76	0·47, 1·23	Age, sex, smoking, education, stomach disorders, family history of stomach cancer, total vegetable consumption

Table 2 *Continued*

First author, year, reference, location	No. of subjects, (age), follow-up	Dietary assessment	Apple intake comparisons	HR/RR	95 % CI	Confounding factors adjusted for
All types of cancer Wang (2009)[34] USA	38 408 cohort female 3234 incident cases (≥45 years) Follow-up 11·5 years	Validated FFQ 131 food items	Apples: ≥2 servings/week (Q4; high) *v.* <1 serving/month (Q1; low)	1·13	0·97, 1·30	Age, race, EI, aspirin, vitamin E, β-carotene, smoking, alcohol, PA, postmenopausal status, hormone replacement therapy, multivitamin, BMI, family history of colorectal/ovary/breast cancer, fruit, vegetables, fibre, folate, saturated fat

HR, hazard ratio; RR, risk ratio; EPIC, European Prospective Investigation into Cancer and Nutrition (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, UK); NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; ESCC, oesophageal squamous cell carcinoma; EAC, oesophageal adenocarcinoma; EI, energy intake; PA, physical activity; CRC, colorectal cancer; OC, oral contraceptives; NSAID, non-steroidal anti-inflammatory drugs.
* *Rosaceae* = apples, peaches, nectarines, plums, pears, strawberries.

Cohort studies were published between 1998 and 2012; nine were conducted in the USA[30,31,34–37,39,40,45] and eight were conducted in Europe[32,33,38,41–44,46]. Pooled analysis were conducted in the USA, Canada, Europe and Australia and included from seven to fourteen prospective studies[47–50]. Seven cohort studies were on lung cancer (1 912 199 cohort and 12 913 incident cases), two on colorectal cancer (796 305 cohort and 6367 incident cases), three on breast cancer (479 219 cohort and 9195 incident cases), and one each on oesophageal, pancreatic, bladder, kidney, endometrial, head–neck, urothelial, stomach and all types of cancer.

Study-specific quality scores are summarized in the supplementary material, Table S1 and Table S2 for case–control and cohort studies, respectively. The range of quality score was from 4 to 8 (median = 6, mean = 6·25, SD = 1·20) and from 7 to 9 (median = 8, mean = 8·1, SD = 0·85) for case–control and cohort studies, respectively. High-quality studies (i.e. those studies that had seven awarded stars) included eight case–control[10,13–15,20,22,23,26] and all twenty-one cohort[30–50] studies.

Apple intake and lung cancer risk

Using the random-effect model, we found that the high intake of apple was significantly associated with a reduced risk of lung cancer in both case–control (OR = 0·75; 95 % CI 0·63, 0·88; $P = 0·001$, $I^2 = 0\,\%$; Fig. 2(a)) and cohort (RR = 0·89; 95 % CI 0·84, 0·94; $P < 0·001$, $I^2 = 68\,\%$; Fig. 2(b)) studies. A pooled analysis performed by combining case–control and cohort studies resulted in a significant 12 % reduction of lung cancer risk (RR = 0·88; 95 % CI 0·83, 0·92; $P < 0·001$, $I^2 = 65\,\%$) and allowed stratification based on both the sex and smoking status of the subjects (Table 3). A significant reduction of lung cancer risk was observed in current smokers (RR = 0·88; 95 % CI 0·77, 1·00; $P < 0·042$, $I^2 = 62\,\%$) and in studies where smokers and non-smokers were considered together (RR = 0·82; 95 % CI 0·72, 0·92; $P = 0·001$, $I^2 = 76\,\%$), while the effect was not statistically significant in never smokers (Table 3). When stratifying the studies according to sex, apple intake was found to be significantly associated with lung cancer risk in males (RR = 0·79; 95 % CI 0·73, 0·85; $P < 0·001$, $I^2 = 3\,\%$) but not in females (RR = 0·92; 95 % CI 0·82, 1·03; $P = 0·146$, $I^2 = 26\,\%$).

Apple intake and risk of digestive tract cancers

A significant reduction of colorectal cancer risk, associated with apple intake, was observed in case–control (OR = 0·56; 95 % CI 0·54, 0·81; $P < 0·001$, $I^2 = 55\,\%$; Fig. 3(a)) but not in cohort (RR = 0·93; 95 % CI 0·79, 1·10; $P = 0·4$, $I^2 = 13\,\%$; Fig. 3(b)) studies. Combining case–control and cohort studies together resulted in a significant preventive effect of apple intake on colorectal cancer (RR = 0·72; 95 % CI 0·59, 0·88; $P = 0·001$, $I^2 = 77\%$; Table 3). No cohort studies were found on oral cavity cancer risk and apple intake; however, the analysis on case–control studies

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showed a significant reduction of risk (OR = 0·25; 95 % CI 0·08, 0·77; $P = 0·015$, $I^2 = 97\,\%$) even if high heterogeneity was observed (Table 3). Instead, no preventive effect of apples was observed on oesophageal cancer risk both in case–control and cohort studies. The pooled analysis of digestive tract cancers (colorectal, oral cavity, oesophageal and stomach) indicated that apple intake was inversely associated with the risk in case–control studies (OR = 0·50; 95 % CI 0·36, 0·69; $P < 0·001$, $I^2 = 90\,\%$) but not in the cohort studies (RR = 0·79; 95 % CI 0·61, 1·01; $P = 0·063$, $I^2 = 61\,\%$).

Apple intake and breast cancer risk

A significant reduction of risk was observed for breast cancer only in case–control (OR = 0·79; 95 % CI 0·73, 0·87; $P < 0·001$, $I^2 = 1\,\%$; Fig. 4(a)) but not in cohort (RR = 0·97; 95 % CI 0·94, 1·01; $P = 0·192$, $I^2 = 0\,\%$; Fig. 4(b)) studies. Pooled analysis resulted in a slightly significant effect (RR = 0·89; 95 % CI 0·79, 1·00; $P = 0·047$, $I^2 = 69\,\%$; Table 3).

Apple intake and cancer risk in other anatomical sites

In the case of prostate cancer, two case–control studies were found useful for the analysis that showed no association with apple intake (OR = 0·93; 95 % CI 0·79, 1·09; $P = 0·369$, $I^2 = 0\,\%$; Table 3). For other anatomical sites, the availability of a single study did not allow the analysis.

Publication bias and sensitivity analysis

No evidence of publication bias could be detected for risk of colorectal, oral cavity, oesophageal and breast cancer. For the lung and overall digestive tract cancers no publication bias was observed in case–control studies. On the other hand, there was some evidence for publication bias regarding the risk of lung cancer in cohort studies and in pooled analysis as shown by both the Egger's regression test and funnel plot asymmetry (not shown). However, no publication bias could be detected by Begg's rank correlation test (the details are shown in Table 3).

Sensitivity analyses investigating the influence of a single study on the lung cancer risk estimate suggested that the risk estimates were not substantially modified by any single study. The lung risk estimates ranged from 0·85 (95 % CI 0·78, 0·91; $P < 0·001$, $I^2 = 36\,\%$) omitting the study of Büchner *et al.*[32] to 0·92 (95 % CI 0·87, 0·99; $P = 0·015$, $I^2 = 67\,\%$) omitting the study of Wright *et al.*[36]. Of note, omitting the study of Büchner *et al.*[32] resulted in the absence of publication bias as evidenced by both Egger's regression ($P = 0·659$) and Begg's rank correlation ($P = 0·528$) tests.

Discussion

To the best of our knowledge, the present meta-analysis is the first one investigating the association between apple consumption and cancer risk in different anatomical sites. Apples are a cheap fruit, easy to store and transport, abundantly present and marketed all year, and therefore are among the most popular fruits in the world. For these reasons, we wondered whether an apple a day keeps the oncologist away[22]. It is important to underline that in some studies the consumption of apple was asked as a single item[10,11,14–20,22,23,25–29,36,40–43] while in others the assessment regarded *Rosaceae*[12,31,35–37] and 'apples and pears' together[13,21,24,32,33,38,44–50]. It would have been interesting to make a stratified analysis as a function of apple intake assessment to highlight the extent to which it influenced the results, but due to the small number of studies this was not possible. Therefore, confounding effects by the intake of other fruits may not be excluded. In particular, when considering the confounding adjusting factors (reported in the last column of Tables 1 and 2) the consumption of other fruit was taken into account only in a few cases[12,16,22,36,44]. Due to the small number of studies recovered for each tumour site and to summarize the overall effect size, the data derived from case–control and cohort studies have also been combined. The pooled results indicated that apple consumption (comparisons between the highest and the lowest category) was significantly associated with lower risk of different cancer types. However, when separately analysed on the basis of study type (case–control *v.* cohort), we generally found that the effect size was more consistent in case–control studies compared with cohort studies. In many cases the analysis of cohort studies did not evidence a significant effect of apple intake on cancer risk, while case–control studies showed a preventive effect. In particular, in the case of lung cancer, the reduction of risk associated with apple intake was statistically highly significant in both case–control and cohort studies. Instead, a significant preventive effect of apples on colorectal, breast and overall digestive tract cancers was found only in case–control studies. Similarly to our finding, a previous meta-analysis reported that prospective studies provide weaker evidence than case–control studies on the association of fruit and vegetable consumption with reduced cancer risk[51]. It is common in meta-analysis to find higher effect size in case–control studies compared with cohort data[52]. In general, case–control studies have several weaknesses and critical points which can lead to an overestimation of the effect. They can be affected by recall and selection bias, producing misclassification of exposure between case and control groups, and the control group may not be representative of the general population. On the other hand, it should be also considered that dietary assessment questionnaires used in prospective studies may be somewhat less accurate than those used in retrospective case–control settings. In the current meta-analysis we also found that case–control studies had lower median quality score than prospective studies (6 *v.* 8), so suggesting that findings derived from

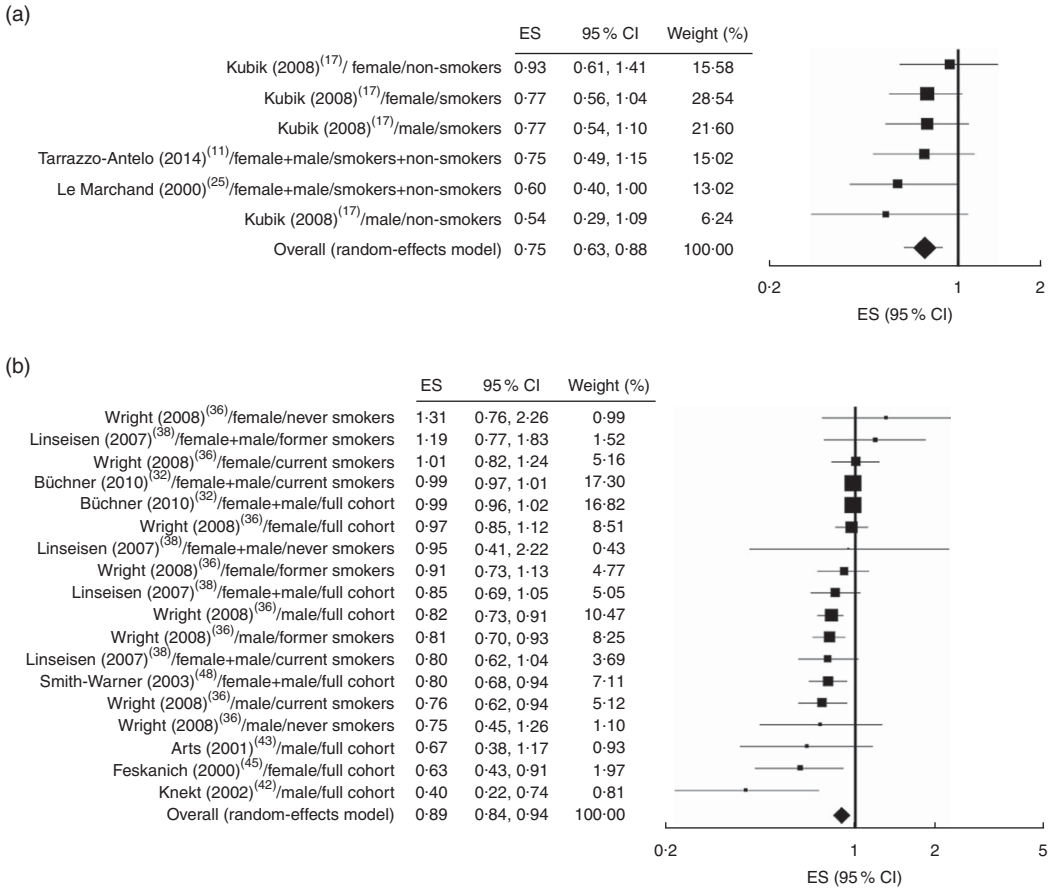

Fig. 2 Forest plots of case–control (a) and cohort (b) studies on apple consumption (highest *v.* lowest category) and lung cancer risk. Squares indicate the study-specific effect size (ES) derived from comparison between the highest and the lowest apple intake (size of square reflects the study's statistical weight, i.e. inverse of variance); horizontal lines indicate 95 % confidence interval; diamond indicates the summary effect size estimate with its corresponding 95 % confidence interval

retrospective studies should be interpreted with caution. In any event, when data from case–control studies were combined with those from cohort studies the meta-analysis showed a significant reduction in risk of lung (12 %), colorectal (28 %), oesophageal (34 %), digestive tract (41 %) and breast (11 %) cancer.

Regardless of the absolute value of the effect size, the inverse association between apple intake and cancer risk is biologically plausible. Apples are a rich source of many different bioactive phenolic compounds (hydroxybenzoic and hydroxycinnamic acids, flavonols, dihydrochalcones, anthocyanids, monomeric and oligomeric flavanols) which may prevent cancer by several mechanisms[7]. First, phenols have a potent antioxidant activity which may protect DNA from oxidative damage. It has been estimated that a 100 g portion of apples has an antioxidant activity equal to 1·500 mg of vitamin C. In addition, *in vitro* studies have demonstrated that apple phenols are able to inhibit tumour cell proliferation, induce cell cycle arrest and apoptosis, suppress angiogenesis and metastasis, modulate carcinogen metabolism and signal transduction pathways, and enhance the immune system. Accordingly, cancer chemopreventive properties of apple *in vivo* have also been demonstrated on several animal models for chemically or genetically induced tumours of the skin, breast and colon, as well as in xenograft models for solid tumours. These data demonstrate that apple constituents may have a systemic effect at the level of different organs, in addition to the more reasonable effect on the gastrointestinal tract.

In this regard, our results on the preventive effect of apples on lung cancer are very consistent in both case–control and cohort studies, even if in this last case a significant publication bias was found by the Egger test. Obviously, smoking status greatly influences lung cancer risk; therefore it would be important to stratify the analysis according to this variable. Unfortunately, only one case–control[17] and two cohort[36,38] studies reported the risk of lung cancer in association with apple intake for smokers and non-smokers separately. Using these few data, we found a statistically significant effect of apple intake on lung cancer risk in current smokers but not in never smokers. Therefore, further studies are necessary to clarify the potential preventive effects of apples on lung cancer in smokers and never smokers. In contrast to lung cancer, the risk of colorectal and breast cancer resulted to

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Table 3 Results of stratified analysis of the risk estimates for the highest compared with the lowest apple intake on the basis of study type and cancer site*,†

	Combined risk estimate			Test of heterogeneity			Publication bias		
Cancer site	Value	95 % CI	*P*	*Q*	I^2 (%)	*P*	*P* (Egger's test)	*P* (Begg test)	References
Lung									
Case–control (*n* 6)‡	0·75	0·63, 0·88	0·001	2·92	0·00	0·713	0·222	0·091	11, 17, 25
Cohort (*n* 18)	0·89	0·84, 0·94	<0·001	52·96	67·90	<0·001	0·003	0·970	32 ,36, 38, 42, 43, 45, 48
Pooled§ (*n* 24)	0·88	0·83, 0·92	<0·001	65·76	65·02	<0·001	<0·001	1·000	
Current smokers (*n* 6)	0·88	0·77, 1·00	0·042	13·02	61·60	0·023	0·035	0·573	17, 32, 36
Never-smokers (*n* 5)	0·88	0·67, 1·15	0·346	4·61	13·70	0·330	0·724	0·624	17, 36, 38
Former smokers (*n* 3)	0·88	0·75, 1·04	0·137	3·10	35·54	0·212	0·041	0·117	36, 38
Smokers + non-smokers (*n* 10)	0·82	0·72, 0·92	0·001	37·75	76·16	<0·001	0·001	0·421	11, 25, 32, 36, 38, 42, 43, 45, 48
Female (*n* 7)	0·92	0·82, 1·03	0·146	8·10	25·95	0·231	0·550	0·881	17, 36, 45
Male (*n* 8)	0·79	0·73, 0·85	<0·001	7·18	2·57	0·410	0·015	0·006	17, 36, 42, 43
Female + male (*n* 9)	0·95	0·90, 1·00	0·053	17·88	55·25	0·022	0·033	0·835	11, 25, 32, 38, 48
Colorectal									
Case–control (*n* 5)	0·66	0·54, 0·81	<0·001	8·89	54·99	0·064	0·594	0·327	14, 16, 20, 22, 28
Cohort (*n* 3)	0·93	0·79, 1·10	0·400	2·30	13·06	0·317	0·169	0·117	39, 49
Pooled§ (*n* 8)	0·72	0·59, 0·88	0·001	30·59	77·11	<0·001	0·252	0·621	
Oral cavity									
Case–control (*n* 3)	0·25	0·08, 0·77	0·015	70·29	97·15	<0·001	0·273	0·117	21, 22, 24
Oesophagus									
Case–control (*n* 2)	0·75	0·5, 1·05	0·091	0·99	0·00	0·319	–	–	15, 22
Cohort (*n* 2)	0·60	0·21, 1·71	0·340	8·28	87·93	0·004	–	–	37
Pooled§ (*n* 4)	0·66	0·41, 1·05	0·078	9·30	67·74	0·026	0·277	0·497	
Overall digestive tract‖									
Case–control (*n* 10)	0·50	0·36, 0·69	<0·001	91·30	90·14	<0·001	0·176	0·128	14–16, 20–22, 24, 28
Cohort (*n* 6)	0·79	0·61, 1·01	0·063	12·84	61·05	0·025	0·069	0·005	37, 39, 46, 49
Polled§ (*n* 16)	0·59	0·47, 0·74	<0·001	136·02	88·97	<0·001	0·048	0·072	
Breast									
Case–control (*n* 5)	0·79	0·73, 0·87	<0·001	4·04	0·88	0·401	0·585	0·327	12, 18, 22, 23, 26
Cohort (*n* 3)	0·97	0·94, 1·01	0·192	0·92	0·00	0·631	0·135	0·117	30, 40, 47
Pooled§ (*n* 8)	0·89	0·79, 1·00	0·047	22·37	68·71	0·002	0·228	0·805	
Prostate									
Case–control (*n* 2)	0·93	0·79, 1·09	0·369	0·19	0·00	0·664	–	–	10, 22

*The analysis was performed when two or more studies were available,
†The risk estimates were calculated using the random-effect model.
‡Number of studies used to calculate the risk is indicated in parentheses.
§Analysis was performed on case–control and cohort studies combined together.
‖Colorectal, oral cavity, oesophageal and stomach cancers.

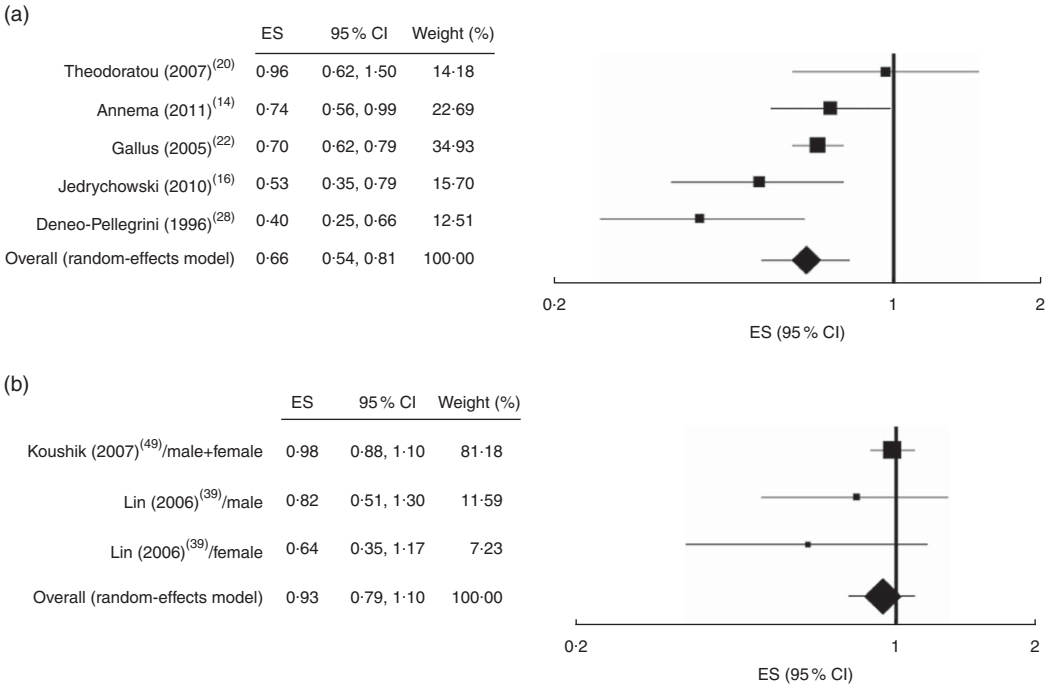

Fig. 3 Forest plots of case–control (a) and cohort (b) studies on apple consumption (highest *v.* lowest category) and colorectal cancer risk. Squares indicate the study-specific effect size (ES) derived from comparison between the highest and the lowest apple intake (size of square reflects the study's statistical weight, i.e. inverse of variance); horizontal lines indicate 95 % confidence interval; diamond indicates summary effect size estimate with its corresponding 95 % confidence interval

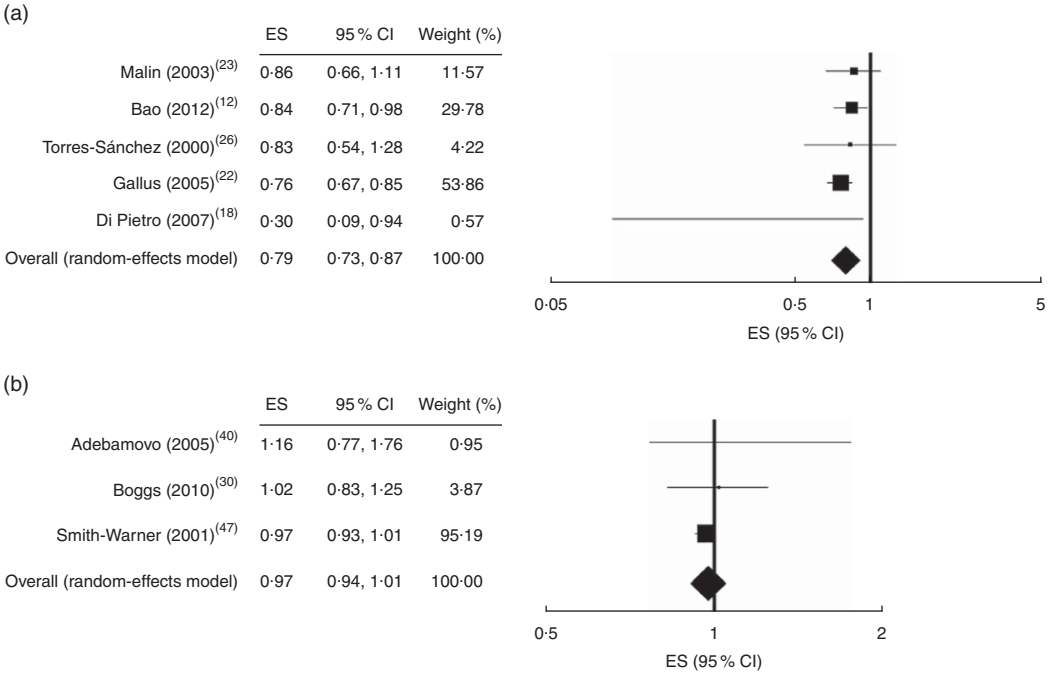

Fig. 4 Forest plots of case–control (a) and cohort (b) studies on apple consumption (highest *v.* lowest category) and breast cancer risk. Squares indicate the study-specific effect size (ES) derived from comparison between the highest and the lowest apple intake (size of square reflects the study's statistical weight, i.e. inverse of variance); horizontal lines indicate 95 % confidence interval; diamond indicates summary effect size estimate with its corresponding 95 % confidence interval

be significantly reduced in case–control studies (34 % and 21 %, respectively) while no significant effect was found in cohort studies. These discrepancies may be in part due to the low number of cohort studies, two for colon–rectum[39,49] and three for breast[30,40,47]. It should be considered, however, that two pooled analyses were

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included in our meta-analysis, one on colorectal cancer[49] and the other on breast cancer[47], which considered eleven and seven cohort studies, respectively. Furthermore, a recent pooled analysis of twenty cohort studies on breast cancer (not included in our meta-analysis) showed a small but significant effect (RR = 0·92; 95 % CI 0·85, 0·99) of apples, together with pears and applesauce, on oestrogen receptor-negative breast cancer[53]. Therefore, as a result of the complexity and variety of the carcinogenic process, it is possible that the stratification of cases according to molecular targets may highlight associations that until now have not been considered. Further studies are needed to investigate these aspects.

There were some limitations in our meta-analysis. Heterogeneity was evident and, in some cases, particularly high. One reason for this could be the wide range of values for the cut-off points for the lowest and highest categories of apple intake. In addition, the number of studies included in the meta-analysis for each cancer type was not large enough to stratify the analysis according to geographic region, sex and adjustment for confounding factors to try to determine the source of heterogeneity. In the case of lung cancer risk, publication bias was also detected in cohort studies. Stratification according to smoking and sex did not clearly reduce both heterogeneity and publication bias in studies on lung cancer. However, the exclusion of one study[32] did not significantly modify the lung cancer risk estimate but eliminated both heterogeneity and publication bias. Although when multiple estimates were available, we abstracted those that adjusted for the most confounding factors, many of the studies included in the analysis varied in the number of potential diet confounding variables (i.e. meat, dairy products, fibre) for which they had not been adjusted. Furthermore, most of the studies were not designed solely to evaluate the association between apple consumption and cancer risk and there were wide variations in dietary assessments of the frequency/quantity of apple intake. For these reasons, in addition to the low number of data available for each cancer site, it was not possible to calculate the dose–response relationship between apple intake and cancer risk in different anatomical organs.

Conclusion

In summary, the current meta-analysis provides convincing evidence supporting the hypothesis of the protective ability of apples in the aetiology of cancer. However, some confounding effects may be present and related to the consumption of other fruit which have not been considered as adjusting factors. Apple consumption was associated with a reduced risk of cancer in the lung, colon–rectum, oral cavity, digestive tract and breast. Further studies will be needed to clarify the effect of apples on cancer risk in other anatomical sites.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S136898001600032X

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