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When is enough, enough? When are more observational epidemiologic studies needed to resolve a research question: illustrations using biomarker-cancer associations

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Abstract

Background: Research reproducibility is vital for translation of epidemiologic findings. However, repeated studies of the same question may be undertaken without enhancing existing knowledge. To identify settings in which additional research is or is not warranted, we adapted research synthesis metrics to determine number of additional observational studies needed to change the inference from an existing meta-analysis.

Methods: The fail-safe number (FSN) estimates number of additional studies of average weight and null effect needed to drive a statistically significant meta-analysis to null ($P \geq 0.05$). We used conditional power to determine number of additional studies of average weight and equivalent heterogeneity to achieve 80% power in an updated meta-analysis to detect the observed summary estimate as statistically significant. We applied these metrics to a curated set of 98 meta-analyses on biomarkers and cancer risk.

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Results: Both metrics were influenced by number of studies, heterogeneity, and summary estimate size in the existing meta-analysis. For the meta-analysis on *H. pylori* and gastric cancer with 15 studies (OR=2.29; 95% CI 1.71–3.05), FSN was 805 studies, supporting futility of further study. For the meta-analysis on dehydroepiandrosterone sulfate and prostate cancer with 7 studies (OR=1.29; 95% CI 0.99–1.69), 5 more studies would be needed for 80% power, suggesting further study could change inferences.

Conclusions: Along with traditional assessments, these metrics could be used by stakeholders to decide whether additional studies addressing the same question are needed.

Impact: Systematic application of these metrics could lead to more judicious use of resources and acceleration from discovery to population-health impact.

Keywords

fail-safe number; conditional power; meta-analyses; epidemiology; observational study; cohort; risk; biomarker; cancer

Introduction

Translation of cancer etiology, risk, prognosis, and prediction biomarkers into prevention and control strategies relies, in part, on the ability to reproduce associations. However, repetitive investigations of *established* biomarker-cancer associations that do not contribute meaningful additional information to the existing evidence base – e.g., fill remaining knowledge gaps, provide substantial clinical or public health support for an association, or have the potential to improve biological understanding – may be inefficient and a waste of resources (1–3).

To address these concerns, we adapted an application of existing clinical trial and research synthesis metrics – the fail-safe number (FSN) (4) and conditional power (5) – to determine whether or not further investigation of cancer relevant biomarkers may provide meaningful contribution to the existing evidence. In its original application, Rosenthal (6) introduced the FSN to quantify the impact of selectively unpublished research on the existing meta-analysis. The FSN indicates the number of unpublished studies with an average null effect (e.g., $P \geq 0.05$) needed to be included in an updated meta-analysis to drive a statistically significant summary estimate in the existing meta-analysis (e.g., $P < 0.05$) to a statistically non-significant summary estimate (e.g., to $P \geq 0.05$) in the updated meta-analysis. We adapted the FSN for observational epidemiology studies to determine whether the inference from an existing meta-analysis for a statistically significant exposure-outcome association, will likely change to a null association with the addition of further research to update the meta-analysis. In its original application, conditional power was used to guide the design of clinical trials based on effect size and sample size of an existing trial or meta-analysis. In the context of observational epidemiology and assuming a statistically non-significant existing meta-analysis, we adapted conditional power calculation to determine the feasibility of conducting the necessary number of future studies with sufficient power to detect a significant association of a certain size in the updated meta-analysis (5).

We applied FSN and conditional power to a collection of 98 existing meta-analyses (7) of associations between non-genomic cancer biomarkers and multiple types of cancer. More detailed illustration of their use is provided using data on a well-established biomarker-cancer relationship (i.e., *H. pylori* and gastric cancer) and an uncertain biomarker-cancer association (i.e., androgens and prostate cancer).

Methods

FSN and conditional power were applied to findings from 98 biomarker-cancer meta-analyses(8–44) (Table 1) published in 37 reports that were curated by Tsilidis et al. after a comprehensive PubMed search of meta-analyses of epidemiologic studies on biomarkers and cancer risk published between 1966 and 2010 (7). The purpose of that study was to evaluate whether evidence of excess statistical significance could be detected in such studies that would be indicative of publication bias.

The 98 meta-analyses included a median of seven studies (range 2–42) and described associations between a diverse range of non-genomic biomarkers and cancer risk including: Insulin-like growth factor(IGF)/insulin markers (21 meta-analyses); sex hormones (13 meta-analyses); dietary markers (31 meta-analyses); inflammatory markers (3 meta-analyses); infectious agents (22 meta-analyses); and environmental markers (8 meta-analyses). The most common cancer sites include breast (28 meta-analyses); prostate (24 meta-analyses); lung (10 meta-analyses); and colorectal (8 meta-analyses). Previously, using the primary study data from the studies included in each of the 98 meta-analyses, Tsilidis et al. (7) calculated summary estimates using fixed-effect and random-effects models and corresponding 95% confidence intervals, and I^2. Based on random-effects models, 44 (45%) of the meta-analyses reported statistically significant summary odds ratios (OR), whereas based on fixed-effect models 54 (55%) of the meta-analyses reported statistically significant summary ORs.

Fail-Safe Number:

For the statistically significant meta-analyses, we used *Rosenberg's* version of the FSN (4) (a refinement of Rosenthal's FSN (6)) to quantify the number of future studies with an average null effect and average weight (i.e., inverse variance), needed to drive the existing meta-analysis summary estimate to null in the updated meta-analysis (for this work: $P \geq 0.05$). To overcome the restriction of statistical significance, we used *Orwin's* FSN (45) to calculate the number of future studies with an average null effect (OR=1.00) needed to reduce the updated summary effect to a range of estimates (OR=1.05; 1.10; 1.25; 1.50; and 2.00) for the updated meta-analysis. Additional details of FSN calculation are presented in Supplemental Methods. FSN is not applicable to non-statistically significant summary estimates.

Conditional power:

For the non-statistically significant meta-analyses, we calculated conditional power to determine the number of future studies needed to achieve sufficient power to detect a statistically significant summary estimate when added to the observed non-statistically

significant meta-analysis (P≥0.05). We set the minimum power to 0.8 and took a pragmatic approach declaring an alternative hypothesis for the updated meta-analysis equivalent to the observed summary OR, and assumed the future studies were of average weight as those included in the observed meta-analysis. Our conditional power analyses were based on two approaches described by Roloff et al. (5) We implemented the first approach in the non-statistically significant fixed-effect meta-analyses, where we assumed that no heterogeneity is present between the studies included in the existing meta-analysis (I^2=0%) and that the future studies will not introduce heterogeneity. In approach 2, focusing on the non-statistically significant random-effects meta-analyses, we fixed the between-study heterogeneity in the future studies to be equivalent to the heterogeneity in the existing meta-analysis. Additional details of conditional power calculation are presented in Supplemental Methods

From the list of 98 meta-analyses, we selected two exemplar scenarios: 1) a well-established causal biomarker-cancer relationship supported by evidence-based classification as a Group 1 carcinogen (i.e., *H. pylori* and gastric cancer risk) (46) and 2) a biomarker-cancer association with strong biological rationale, but several methodologic concerns leading to an uncertain biomarker-cancer association (i.e., androgens and prostate cancer). We provide these two examples both to describe the application of these adapted methods and how their use can be used in practice to inform the need for future research to be able to fill knowledge gaps and improve biological understanding. For both scenarios, we interpret the number of future studies needed determined by FSN for *H. pylori* and gastric cancer or by conditional power for androgens and prostate cancer within the context of the existing evidence (e.g., the number, sample size, and heterogeneity of the findings).

We calculated *Rosenberg's* and *Orwin's* FSNs and the two conditional power approaches in STATA version 13 (STATA Corp, College Station, TX).

Results

FSN.

Among the 54 statistically significant fixed-effect (median number of studies 9 [range 2–42]; median I^2=42%) and 44 statistically significant random-effects (median number of studies 9 [range 2–42]; median I^2=36%) meta-analyses, median FSN (*Rosenberg*) was 31.5 studies (range 3.2–24,939) for the fixed-effect meta-analyses, and 31.1 studies (range 3.2–3,464) for the random-effects meta-analyses.

The influence of between-study heterogeneity on *Rosenberg's* FSN is illustrated by comparing the FSN between the fixed-effect and random-effects summary estimates from the same meta-analysis (SFigure 1). The median FSN was larger for meta-analyses with extreme heterogeneity (I^2>80% (47)); 1497 and 148 for fixed-effect and random-effects meta-analyses, respectively, compared to 53 and 45 for fixed-effect and random-effects meta-analyses with low heterogeneity (I^2: 1–29% (47)). The FSN was larger for the fixed-effect than for the random-effects meta-analyses, which is consistent with the assumption of no between-study heterogeneity in fixed-effect meta-analyses that results in more precise summary estimates (48) (SFigure 1). Among meta-analyses with similar between-study

heterogeneity (0%, 1–29%, 30–59%, 60–80%, >80%), meta-analyses that included more studies tended to have a higher FSN (SFigure 2) as a result of more precise summary estimates.

Rosenberg's FSN was larger when the summary estimates observed in the existing meta-analyses were higher (SFigure 3). The influence of summary estimate size in the existing meta-analysis and in the future studies is further illustrated with *Orwin's* FSN, which does not take into account within- or between-study heterogeneity. Therefore, we only considered the values of *Orwin's* FSN for fixed-effect meta-analyses. *Orwin's* FSN was larger for smaller updated summary estimates (SFigure 4). To reduce the updated summary OR to 1.05 among 38 meta-analyses with an existing summary OR>1.05, the median of *Orwin's* FSN was 271 studies, whereas to reduce the updated summary OR to 2.00 among meta-analyses with an existing summary OR>2.00 the median FSN was 33 studies. As for *Rosenberg's* FSN, which is based on statistical significance, *Orwin's* FSN, which is based on effect size, also indicates that a larger number of future studies is required for existing meta-analyses with larger as opposed to smaller summary ORs.

Conditional power.

We used two approaches under a variety of assumptions to conduct conditional power analysis. In the first approach, we assumed no between-study heterogeneity in the existing and updated meta-analyses, and accordingly, used only the 18 fixed-effect meta-analyses with a statistically non-significant summary OR>1.01. With a median power of 15% (range 0.5–50%) for the existing meta-analyses, a median of 78 studies (range 4–994) of average weight with no between-study heterogeneity would need to be included in the updated meta-analysis to achieve 80% power to detect the summary OR as statistically significant.

In the second approach, we assumed equivalent between-study heterogeneity in the future studies as in the existing meta-analysis, and accordingly used the 21 random-effects meta-analyses with a statistically non-significant summary OR>1.01. With a median power of 21% (range 6–47%) for the existing meta-analyses, a median of 103 studies (range 5–6,656) of average weight and equivalent between-study heterogeneity as in the existing meta-analysis would need to be included in the updated meta-analysis to achieve 80% power to detect the summary OR as statistically significant.

The greater number of future studies required to achieve 80% for the random-effects compared with fixed-effect meta-analysis is consistent with their differing assumptions about between-study heterogeneity incorporated into the two approaches (SFigure 5). By taking into account the between-study heterogeneity, our second approach incorporated additional uncertainty into the summary estimates, thereby increasing the number of future studies needed. In the both fixed-effect and random-effects meta-analyses, the number of future studies needed was smaller for larger than for smaller summary estimates (SFigure 5).

Application of the FSN: H. pylori and gastric cancer.

In 1994, the International Agency for Research on Cancer (IARC) classified *Helicobacter pylori* as a Group 1 carcinogen (46). At the time, the evidence supporting IARC's classification included four cohort studies and nine case-control studies of *H. pylori*

infection and gastric cancer risk. Since the initial classification, the accumulation of evidence is sufficient that the relationship is now considered well established. This is reflected in the greater than 2-fold increase in risk of gastric cancer described in the meta-analysis of 15 studies with more than 5,000 cases and controls reported by Huang et al. (33) *Rosenberg's* FSN indicates 805 future studies would be required to reduce the reported fixed-effect summary OR of 2.05 (95% CI 1.79–2.35; I^2=76%) to null (P≥0.05) and 224 future studies based on the random-effects meta-analysis (summary OR=2.29; 95% CI 1.71–3.05; I^2=76%). Based on *Orwin's* FSN, a total of 615 future studies averaging null effect (OR=1.00) would be required to drive the observed fixed-effect summary OR of 2.05 to an essentially null OR of 1.05. The implementation of each FSN to the example of *H. pylori* and gastric cancer illustrates the futility of further investigation of the association between *H. pylori* and gastric cancer, while the large between-study heterogeneity (I^2=76%) suggests the need for further subgroup analysis to determine sources of heterogeneity (e.g., method of detection of *H. pylori* infection, adjustment for confounding, or geographic/ethnic differences in strength of the association). To this end, the geographic and ethnic differences in the distribution of gastric cancer led to further investigations that revealed a stronger association between *H. pylori* infection and gastric cancer in studies conducted in populations with diets high in salt-preserved foods, suggesting dietary salt may modify the pathogenic effect of *H. pylori* infection on gastric cancer (49, 50). The role of a high salt diet as a potential modifier of the effect of *H. pylori* is supported by additional laboratory research that identified cagA gene expression in *H. pylori*, a marker of higher risk of gastric cancer, is upregulated by dietary salt intake (51). These findings further illustrate the importance of examining subgroups or different populations once the main effect of the etiologic cancer biomarker has been established, especially in the context of extreme heterogeneity which can help identify high-risk populations and can provide additional understanding of the underlying biology of the biomarker cancer association (e.g., effect modification).

Application of conditional power: Androgens and prostate cancer.

In 1993, the Prostate Cancer Prevention Trial was launched to test the hypothesis that finasteride, a drug that blocks the conversion of testosterone into dihydrotestosterone (DHT), can prevent prostate cancer (52). The trial was stopped early in 2003 when an interim analysis found a 25% reduction in the period prevalence of prostate cancer in the treatment group receiving finasteride (53). This finding provided additional evidence supporting the underlying hypothesis that DHT is an etiologic factor in prostate cancer. However, several methodological challenges encountered in population-based epidemiologic investigations including adequacy of measuring circulating hormones, difficulty integrating multiple components of the androgen pathway, difficulty in incorporating clinical and population health important outcomes, and detection bias (e.g., differential opportunity to be screened with PSA by exposure; and differential detection of prostate cancer in PSA-based prostate cancer screening due to the association between androgens and PSA concentration), have contributed to the inconsistent reports on the associations between circulating androgens and prostate cancer incidence (54). Using study-specific estimates for components in the androgen pathway and prostate cancer from a pooled analysis of harmonized primary data, (43) Tsilidis et al. (7) calculated fixed-effect and random-effects summary estimates (Table

2). For the six components of the androgen pathway that were not statistically significant in fixed-effect meta-analyses (with I^2=0% and a median number of studies of 8.5), conditional power indicated that 18 to 1173 future studies of average weight as those included in the existing meta-analysis would be required to achieve 80% power to detect the summary OR in the updated meta-analysis (Table 2). For these comparisons, the large number of future studies needed to achieve sufficient power – more than twice as many studies as included in the existing meta-analyses – of the same average weight – totaling tens of thousands of cases and controls among the future studies (Table 2) – may not be within reach of existing resources, and points to a situation where further research should be aimed at overcoming the methodologic challenges mentioned above (54) to fill important evidence gaps with respect to androgens and prostate cancer.

In the case of the random-effects meta-analysis with 7 included studies evaluating the association between dehydroepiandrosterone sulfate (DHEA-S) and prostate cancer (summary OR=1.29; 95% CI 0.99 to 1.68; I^2=17%), the 5 future studies required to achieve 80% power to detect the observed summary OR may be within reach of existing resources, and points to a scenario where additional research could provide a meaningful contribution to the existing meta-analysis. However, we caution against the inappropriate interpretation of applying conditional power to the example of DHEA-S and prostate cancer incidence. Our approach assumed that the number of future studies are of the average weight of those already included in the existing meta-analysis and that they will not introduce additional between-study heterogeneity into the updated meta-analysis. However, this assumption may not be realistic; with respect to molecular epidemiologic investigations, measurement error in the index biomarker assay may introduce between-study heterogeneity. Further, relying on the number of needed studies does not guarantee that a future study will be informative. Whether to conduct future studies on DHEA-S and prostate cancer must also take into consideration the composition of the existing evidence base (e.g., existing study population characteristics and prostate cancer case mix) and failure to consider the methodological issues previously cited as factors leading to inconsistent associations could also lead to uninformative research.

Discussion

We adapted two established metrics – the fail-safe number (FSN) (4) and conditional power (5) – to quantify the impact of future investigations on the inferences drawn in existing meta-analyses. Both metrics provide a heuristic approach to inform whether continued investigation is warranted versus sufficient evidence is available to establish or refute an exposure-outcome association. Our motivation to adapt the application of these metrics is to be able to quantify the impact of further investigation of the same association as the primary research question. However, the application of these metrics should not be interpreted as stopping research all together, but rather, to focus future research to address current evidence gaps and improve biologic understanding of the biomarker-cancer association by evaluating new or improved methods to measure the biomarker or using other markers correlated and more specific to the studied biomarker, evaluating clinically meaningful outcomes, and reducing heterogeneity and imprecision in the observed associations by investigating the biomarker-cancer relationship in important subpopulations. When further research does not

add information to the existing literature, unnecessary and wasteful research may be undertaken (55). We envision the application of these metrics along with traditional assessments of study quality (e.g., STROBE,(56) PRISMA,(57)) causal criteria (58), and remaining knowledge gaps (e.g., subgroup associations) by stakeholders engaged in translational epidemiologic research including principal investigators, funding agencies, grant reviewers, journal editors, and peer-reviewers to make more informed decisions about the need for additional research. While our application of FSN and conditional power focused on observational studies of etiologic biomarkers and cancer risk, these methods are equally applicable to other epidemiologic study designs including randomized trials as well as non-biomarker exposures and other important outcomes such as mortality, and prognosis.

FSN can be calculated using several common meta-analysis software packages and calculation of conditional power is straightforward (See Supplemental Methods) but requires a number of assumptions (e.g., heterogeneity, effect size, and study weights) that influence how the corresponding metrics are interpreted, thus informing the impact of future research. We applied these metrics to 98 meta-analyses of observational epidemiologic studies evaluating the associations between non-genomic biomarkers and cancer risk to demonstrate the ability of these metrics to identify situations where future research may or may not provide a meaningful contribution to an updated meta-analysis. When adapting the application of these metrics, the patterns of the output of the FSN and conditional power analysis are consistent with the underlying computation of each metric. For example, FSN appears to increase with decreasing heterogeneity, increasing number of included studies, and increasing magnitude of summary estimates. For conditional power, the number of additional studies appears to decrease with increasing magnitude of summary estimates.

To our knowledge no method has been introduced to directly quantify the expected impact of further observational epidemiologic research on the current evidence base. While our motivation was to explore whether the FSN and conditional power could be used to quantify the impact of future research, additional work is needed to incorporate these metrics into a formal framework for deciding whether additional epidemiologic studies addressing the same question are needed. Such a framework might include cutpoints or ranges for defining whether the number of future studies needed is too large to make additional work worthwhile. We do not envision that the framework would rely on cutpoints alone: considerations that could be incorporated into the framework beyond a cutpoint might include feasibility and cost as well as implications for policy, and clinical and public health recommendations. Such a framework could encompass aspects of the Value of Information approach to deciding cost-effectiveness, which has been described for improving research prioritization and reducing waste (59).

We recognize that application of these adapted methods to existing meta-analyses is not the only strategy to minimizing the problem of repetitive research. Facilitating and encouraging the publication of null results that can be included in meta-analyses such that the null results are interpreted alongside the relevant evidence is a direct way investigators and stakeholders can minimize the production of redundant uninformative research (60). An alternative approach is a coordinated effort among individual investigators to determine which exposures require additional investigations, to share and pool their data and biospecimens, to

standardize an exposure's measurement and harmonize the outcome and covariate data, all while ensuring optimal study design and minimizing selection and information bias. Using this approach, research on particular exposures is prioritized through consensus, exposure-outcome associations can be investigated in subpopulations of the pooled studies, and power is maximized. This practice-based approach has been used over the past 15 years by large consortia, including the NCI Cohort Consortium (>50 cohorts with 7 million participants) (https://epi.grants.cancer.gov/Consortia/cohort.html#overview) and the Early Detection Research Network (https://edrn.nci.nih.gov) both supported by the National Cancer Institute (NCI), and the Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborative Group (35 studies with biomarker data on 23,000 men with prostate cancer and 35,000 controls) (https://www.ceu.ox.ac.uk/research/endogenous-hormones-nutritional-biomarkers-and-prostate-cancer). We view the approach that we describe herein as complementary to the practice-based approach.

In summary, we show how FSN and conditional power can be adapted to quantify the impact of future investigations of a specified exposure and outcome on the current evidence base summarized in the corresponding meta-analysis. To illustrate the utility of these approaches, we applied them to meta-analyses of biomarkers and cancer risk. The systematic application of these metrics by researchers, funding agencies, and grant reviewers when considering future research, journal editors, and peer-reviewers when considering the novelty and impact of submitted manuscripts, could lead to more judicious use of resources and acceleration along the translational continuum from discovery to population-health impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Results for Rosenberg's and Orwin's FSN and conditional power for the 98 meta-analysis

Area	Author & Year	Cancer	Biomarker	No. of studies	No. cases & controls	I^2	Fixed-effect				Random-effects		
							OR (95% CI)	FSN^1	FSN^2	M^3	OR (95% CI)	FSN^1	M^4
Diet	Chen 2010(8)	BrCA	$1\alpha,25(OH)_2$ vitamin D	3	3627	47	1.02 (0.81–1.29)	NA	NA	858	0.99 (0.68–1.44)	NA	27210
Diet	Saadatian-Elahi 2004(9)	BrCA	Arachidonic acid	5	2226	0	0.89 (0.65–1.22)	NA	NA	79	0.89 (0.65–1.22)	NA	181
Diet	Saadatian-Elahi 2004(9)	BrCA	Linoleic acid	8	3081	60	0.88 (0.69–1.12)	NA	NA	67	0.85 (0.57–1.26)	NA	457
Diet	Saadatian-Elahi 2004(9)	BrCA	MUFA	5	2291	67	1.33 (0.98–1.81)	NA	NA	4	1.44 (0.82–2.53)	NA	31
Diet	Saadatian-Elahi 2004(9)	BrCA	Palmitic acid	7	2802	59	1.04 (0.81–1.35)	NA	NA	621	1.05 (0.69–1.58)	NA	6656
Diet	Saadatian-Elahi 2004(9)	BrCA	Palmitoleic acid	2	798	81	1.09 (0.68–1.74)	NA	NA	123	1.26 (0.41–3.89)	NA	301
Diet	Saadatian-Elahi 2004(9)	BrCA	SFA	6	2570	0	1.05 (0.79–1.39)	NA	NA	410	1.05 (0.79–1.39)	NA	1430
Diet	Saadatian-Elahi 2004(9)	BrCA	Stearic acid	7	2802	14	0.93 (0.71–1.23)	NA	NA	200	0.93 (0.69–1.26)	NA	937
Diet	Saadatian-Elahi 2004(9)	BrCA	α-Linolenic acid	8	3444	39	0.82 (0.65–1.03)	NA	NA	12	0.80 (0.59–1.08)	NA	39
Diet	Saadatian-Elahi 2004(9)	BrCA	n-3 PUFA	8	2946	37	0.79 (0.60–1.03)	NA	NA	11	0.79 (0.56–1.11)	NA	51
Diet	Saadatian-Elahi 2004(9)	BrCA	n-6 PUFA	7	2667	16	0.75 (0.55–1.03)	NA	NA	36	0.75 (0.53–1.06)	NA	369
Diet	Chen 2010(8)	BrCA	25(OH) vitamin D	7	11330	86	0.58 (0.51–0.66)	230	75	NA	0.55 (0.38–0.80)	29	NA
Diet	Saadatian-Elahi 2004(9)	BrCA	Docosahexanoic acid	7	3262	36	0.76 (0.59–0.99)	5	106	NA	0.73 (0.53–1.02)	NA	9
Diet	Saadatian-Elahi 2004(9)	BrCA	Eicosapentanoic acid	5	2291	0	0.91 (0.87–0.95)	48	88	NA	0.91 (0.87–0.95)	48	NA
Diet	Buck 2010(10)	BrCA	Enterolactone	12	7710	71	0.84 (0.74–0.96)	24	200	NA	0.79 (0.61–1.02)	NA	14
Diet	Larsson 2007(11)	BrCA	Folate	6	3584	41	0.69 (0.53–0.90)	18	79	NA	0.67 (0.46–1.00)	6	NA
Diet	Saadatian-Elahi 2004(9)	BrCA	Oleic acid	9	3723	70	0.83 (0.71–0.98)	14	144	NA	0.99 (0.70–1.38)	NA	184370
Diet	Larsson 2010(12)	CRC	Vitamin B6	4	2307	0	0.52 (0.38–0.71)	31	39	NA	0.52 (0.38–0.71)	31	NA
Diet	Yin 2009(13)	Colon CA	25(OH) vitamin D	7	2944	46	0.77 (0.59–1.00)	7	103	NA	0.78 (0.53–1.13)	NA	46
Diet	Gallicchio 2008(14)	Lung CA	α-carotene	5	5618	53	0.91 (0.69–1.19)	NA	NA	65	0.88 (0.59–1.33)	NA	438
Diet	Gallicchio 2008(14)	Lung CA	B-cryptoxanthin	5	5618	75	0.87 (0.62–1.21)	NA	NA	44	0.82 (0.40–1.69)	NA	529
Diet	Gallicchio 2008(14)	Lung CA	Lutein/zeaxanthin	4	5066	11	0.95 (0.68–1.33)	NA	NA	342	0.95 (0.67–1.36)	NA	1192
Diet	Zhuo 2004(15)	Lung CA	Selenium	6	2687	42	0.80 (0.63–1.02)	NA	NA	6	0.77 (0.56–1.08)	NA	17
Diet	Gallicchio 2008(14)	Lung CA	B-carotene	10	37629	41	0.83 (0.73–0.94)	31	160	NA	0.84 (0.66–1.07)	NA	36
Diet	Gallicchio 2008(14)	Lung CA	Carotenoids	4	7803	45	0.70 (0.50–0.97)	5	53	NA	0.70 (0.44–1.11)	NA	12
Diet	Gallicchio 2008(14)	Lung CA	Lycopene	4	5294	0	0.71 (0.51–0.99)	5	54	NA	0.71 (0.51–0.99)	5	NA
Diet	Yin b 2009(16)	PrCA	25(OH) vitamin D	11	7806	26	1.03 (0.97–1.10)	NA	NA	82	1.03 (0.95–1.11)	NA	536
Diet	Collin 2010(17)	PrCA	Folate	7	9920	39	1.04 (0.98–1.11)	NA	NA	25	1.11 (0.96–1.28)	NA	17
Diet	Collin 2010(17)	PrCA	Total Homocysteine	4	7015	14	0.93 (0.74–1.17)	NA	NA	77	0.91 (0.70–1.19)	NA	123

Area	Author & Year	Cancer	Biomarker	No. of studies	No. cases & controls	I^2	Fixed-effect				Random-effects		
							OR (95% CI)	FSN[1]	FSN[2]	M[3]	OR (95% CI)	FSN[1]	M[4]
Diet	Collin 2010(17)	PrCA	Vitamin B12	6	9401	45	1.09 (1.03–1.14)	24	127	NA	1.10 (1.01–1.19)	10	NA
Diet	Simon 2009(18)	PrCA	α-Linolenic acid	6	2361	16	1.51 (1.17–1.94)	26	181	NA	1.54 (1.16–2.06)	21	NA
Environment	Khanjani 2007(19)	BrCA	Cis-nonachlor	3	1387	0	1.09 (0.72–1.64)	NA	NA	137	1.09 (0.72–1.64)	NA	290
Environment	Lopez-Cervantes 2004(20)	BrCA	DDT	24	11369	17	0.97 (0.87–1.09)	NA	NA	668	0.97 (0.85–1.11)	NA	8663
Environment	Khanjani 2007(19)	BrCA	Dieldrin	5	3223	43	1.18 (0.89–1.58)	NA	NA	26	1.15 (0.77–1.69)	NA	288
Environment	Khanjani 2007(19)	BrCA	Trans-nonachlor	6	3248	0	0.86 (0.68–1.07)	NA	NA	23	0.86 (0.68–1.07)	NA	35
Environment	Khanjani 2007(19)	BrCA	Oxychlordane	5	2718	51	0.75 (0.57–0.98)	4	73	NA	0.77 (0.51–1.14)	NA	38
Environment	Veglia 2008(21)	CA (cur smokers)	DNA adducts	8	916	94	3.88 (3.31–4.54)	1146	628	NA	3.76 (1.75–8.05)	39	NA
Environment	Veglia 2008(21)	CA (for smokers)	DNA adducts	7	632	0	0.94 (0.71–1.25)	NA	NA	291	0.94 (0.71–1.25)	NA	1041
Environment	Veglia 2008(21)	CA (nev smokers)	DNA adducts	9	564	79	1.20 (0.88–1.64)	NA	NA	41	1.64 (0.72–3.77)	NA	103
IGF/insulin	Pisani 2008(22)	BrCA	C-peptide	11	3517	64	1.26 (1.07–1.48)	27	269	NA	1.35 (1.01–1.81)	11	NA
IGF/insulin	Morris 2006(23)	CRC	IGFBP-3	7	3501	60	1.00 (0.77–1.30)	NA	NA	NA	0.98 (0.64–1.51)	NA	47178
IGF/insulin	Pisani 2008(22)	CRC	C-peptide	12	5542	54	1.36 (1.15–1.62)	64	322	NA	1.51 (1.14–1.99)	39	NA
IGF/insulin	Pisani 2008(22)	CRC	Glucose	11	1381129	47	1.19 (1.07–1.32)	49	257	NA	1.28 (1.06–1.54)	26	NA
IGF/insulin	Rinaldi 2010(24)	CRC	IGF-1	11	7828	0	1.07 (1.01–1.14)	17	230	NA	1.07 (1.01–1.14)	17	NA
IGF/insulin	Morris 2006(23)	CRC	IGF-2	3	1685	0	1.95 (1.26–3.00)	11	117	NA	1.95 (1.26–3.00)	11	NA
IGF/insulin	Pisani 2008(22)	Endometrial CA	C-peptide	4	862	69	1.09 (0.74–1.62)	NA	NA	141	1.18 (0.57–2.43)	NA	642
IGF/insulin	Chen 2009(25)	Lung CA	IGF-1	6	12515	41	1.05 (0.80–1.37)	NA	NA	361	0.98 (0.68–1.41)	NA	21602
IGF/insulin	Chen 2009(25)	Lung CA	IGFBP-3	6	12515	67	0.89 (0.68–1.15)	NA	NA	54	0.96 (0.59–1.56)	NA	10376
IGF/insulin	Pisani 2008(22)	Pancreas CA	C-peptide	2	692	0	1.70 (1.11–2.61)	4	68	NA	1.70 (1.11–2.61)	4	NA
IGF/insulin	Pisani 2008(22)	Pancreas CA	Glucose	5	1334539	0	1.98 (1.67–2.35)	152	198	NA	1.98 (1.67–2.35)	152	NA
IGF/insulin	Rowlands 2009(26)	PrCA	IGFBP-1	3	1553	92	0.93 (0.80–1.09)	NA	NA	72	1.20 (0.65–2.22)	NA	251
IGF/insulin	Rowlands 2009(26)	PrCA	IGFBP-2	5	2670	78	1.07 (0.95–1.21)	NA	NA	36	1.18 (0.90–1.54)	NA	56
IGF/insulin	Rowlands 2009(26)	PrCA	IGFBP-3	29	17160	81	0.97 (0.93–1.01)	NA	NA	80	0.88 (0.79–0.98)	57	NA
IGF/insulin	Rowlands 2009(26)	PrCA	IGF-1	42	19347	88	1.18 (1.14–1.23)	1497	974	NA	1.21 (1.07–1.36)	159	NA
IGF/insulin	Rowlands 2009(26)	PrCA	IGF-1/BP-3	11	9677	80	1.07 (1.02–1.13)	30	230	NA	1.10 (0.97–1.24)	NA	46
IGF/insulin	Rowlands 2009(26)	PrCA	IGF-2	10	2797	77	1.24 (1.12–1.36)	81	242	NA	1.17 (0.93–1.47)	NA	75
IGF/insulin	Key 2010(27)	postmenopausal BrCA	IGF-1	15	8185	0	1.30 (1.13–1.49)	92	385	NA	1.30 (1.13–1.49)	92	NA
IGF/insulin	Key 2010(27)	postmenopausal BrCA	IGFBP-3	15	8012	31	1.21 (1.04–1.41)	32	357	NA	1.22 (1.01–1.49)	16	NA
IGF/insulin	Key 2010(27)	premenopausal BrCA	IGFBP-3	11	5927	0	0.99 (0.83–1.19)	NA	NA	7367	0.99 (0.83–1.19)	NA	50352
IGF/insulin	Key 2010(27)	premenopausal BrCA	IGF-1	11	6033	29	1.18 (1.00–1.40)	10	255	NA	1.21 (0.98–1.49)	NA	12
Infection	Gutierrez 2006(28)	Bladder CA	HPV (DNA)	13	657	6	2.29 (1.37–3.84)	53	597	NA	2.30 (1.33–4.00)	45	NA

Area	Author & Year	Cancer	Biomarker	No. of studies	No. cases & controls	I^2	Fixed-effect				Random-effects		
							OR (95% CI)	FSN[1]	FSN[2]	M[3]	OR (95% CI)	FSN[1]	M[4]
Infection	Gutierrez 2006(28)	Bladder CA	HPV (no DNA)	3	379	0	2.98 (1.65–5.40)	18	180	NA	2.98 (1.65–5.40)	18	NA
Infection	Zhao 2008(29)	CRC	*H. pylori*	14	3581	58	1.41 (1.22–1.65)	127	391	NA	1.49 (1.16–1.90)	57	NA
Infection	Mandelblatt 1999(30)	Cervical CA	HPV	12	3657	27	8.07 (6.49–10.0)	2338	1978	NA	8.08 (6.04–10.8)	1249	NA
Infection	Zhang 1994(31)	Cervical CA	*T. vaginalis*	2	65764	0	1.88 (1.29–2.74)	9	75	NA	1.88 (1.29–2.74)	9	NA
Infection	Islami 2008(32)	ESCC	*H. pylori*	9	3664	73	1.08 (0.92–1.27)	NA	NA	73	1.10 (0.78–1.55)	NA	1356
Infection	Islami 2008(32)	ESCC	cagA (*H. pylori)*	4	2327	0	1.01 (0.79–1.27)	NA	NA	NA	1.01 (0.79–1.27)	NA	NA
Infection	Islami 2008(32)	Esophageal adeno CA	*H. pylori*	13	3730	15	0.56 (0.48–0.67)	275	136	NA	0.57 (0.47–0.69)	207	NA
Infection	Islami 2008(32)	Esophageal adeno CA	cagA (*H. pylori)*	5	1472	17	0.41 (0.29–0.59)	54	37	NA	0.41 (0.28–0.62)	42	NA
Infection	Huang 2003(33)	Gastric CA	*H. pylori*	15	5054	76	2.05 (1.79–2.35)	805	615	NA	2.29 (1.71–3.05)	224	NA
Infection	Huang 2003(33)	Gastric CA	cagA (*H. pylori)*	10	3831	85	2.65 (2.29–3.05)	888	531	NA	2.87 (1.95–4.22)	137	NA
Infection	Zhuo 2008(34)	Laryngeal CA	*H. pylori*	3	357	0	2.02 (1.27–3.23)	10	121	NA	2.02 (1.27–3.23)	10	NA
Infection	Hobbs 2006(35)	Larynx CA	HPV	8	1133	50	1.71 (1.11–2.64)	17	281	NA	2.01 (0.96–4.22)	NA	6
Infection	Donato 1998(36)	Liver CA	HBV (HCV-)	28	9199	86	17.9 (15.7–20.5)	24939	10279	NA	21.9 (14.9–32.3)	3464	NA
Infection	Donato 1998(36)	Liver CA	HBV + HCV	9	2437	37	65.0 (35.0–121)	784	12315	NA	61.2 (27.0–139)	440	NA
Infection	Donato 1998(36)	Liver CA	HCV (HBV-)	26	7694	86	16.8 (14.1–20.0)	13151	9822	NA	20.3 (12.2–33.7)	1924	NA
Infection	Zhuo 2009(37)	Lung CA	*H. pylori*	4	430	79	2.31 (1.46–3.65)	22	185	NA	3.24 (1.11–9.41)	6	NA
Infection	Hobbs 2006(35)	Oral CA	HPV	8	3976	62	1.68 (1.36–2.08)	76	274	NA	1.99 (1.17–3.38)	17	NA
Infection	Hobbs 2006(35)	Oropharynx CA	HPV	5	2199	56	3.01 (2.11–4.30)	93	300	NA	4.31 (2.07–8.95)	35	NA
Infection	Taylor 2005(38)	PrCA	HPV	9	4864	35	1.37 (1.11–1.69)	31	246	NA	1.52 (1.12–2.06)	23	NA
Infection	Hobbs 2006(35)	Tonsil CA	HPV	8	380	0	15.1 (6.78–33.4)	173	2471	NA	15.1 (6.78–33.4)	173	NA
Infection	Wang 2007(39)	early Gastric CA	*H. pylori*	15	16698	83	4.83 (4.27–5.48)	4639	1467	NA	3.38 (2.15–5.32)	197	NA
Inflammation	Heikkila 2009(40)	CA	Interleukin-6	4	6785	21	1.01 (0.92–1.11)	NA	NA	718	1.01 (0.90–1.12)	NA	3321
Inflammation	Heikkila 2009(40)	CA	C-reactive protein	14	74545	73	1.09 (1.05–1.13)	150	299	NA	1.10 (1.02–1.18)	35	NA
Inflammation	Tsilidis 2008(41)	CRC	C-reactive protein	8	39145	51	1.10 (1.02–1.18)	20	172	NA	1.12 (1.01–1.25)	12	NA
Sex hormones	Barba 2009(42)	PrCA	2OHE1	2	536	0	0.76 (0.45–1.28)	NA	NA	13	0.76 (0.45–1.28)	NA	15
Sex hormones	Roddam 2008(43)	PrCA	A-diol G	8	5488	24	1.12 (0.96–1.31)	NA	NA	17	1.15 (0.95–1.38)	NA	28
Sex hormones	Roddam 2008(43)	PrCA	D4	6	4211	0	1.02 (0.85–1.21)	NA	NA	994	1.02 (0.85–1.21)	NA	3995
Sex hormones	Roddam 2008(43)	PrCA	DHEA-S	7	3024	17	1.22 (0.98–1.53)	NA	NA	8	1.29 (0.99–1.68)	NA	5
Sex hormones	Roddam 2008(43)	PrCA	DHT	7	2455	0	0.88 (0.69–1.11)	NA	NA	41	0.88 (0.69–1.11)	NA	80
Sex hormones	Roddam 2008(43)	PrCA	E2	9	5225	0	0.92 (0.78–1.09)	NA	NA	62	0.92 (0.78–1.09)	NA	162
Sex hormones	Roddam 2008(43)	PrCA	Free E2	8	4778	0	0.97 (0.82–1.16)	NA	NA	1173	0.97 (0.82–1.16)	NA	5279
Sex hormones	Roddam 2008(43)	PrCA	Free T	14	9365	0	1.12 (0.98–1.27)	NA	NA	18	1.12 (0.98–1.27)	NA	20

Area	Author & Year	Cancer	Biomarker	No. of studies	No. cases & controls	I^2	Fixed-effect				Random-effects		
							OR (95% CI)	FSN[1]	FSN[2]	M[3]	OR (95% CI)	FSN[1]	M[4]
Sex hormones	Roddam 2008(43)	PrCA	T	17	10324	0	0.98 (0.87–1.10)	NA	NA	502	0.98 (0.87–1.10)	NA	3602
Sex hormones	Barba 2009(42)	PrCA	16α-OHE1	2	536	0	1.82 (1.08–3.05)	3	73	NA	1.82 (1.08–3.05)	3	NA
Sex hormones	Barba 2009(42)	PrCA	2OHE1/16α-OHE1	2	536	0	0.52 (0.31–0.89)	4	19	NA	0.52 (0.31–0.89)	4	NA
Sex hormones	Roddam 2008(43)	PrCA	SHBG	15	9702	0	0.86 (0.76–0.97)	32	249	NA	0.86 (0.76–0.97)	32	NA
Sex hormones	Key 2002(44)	postmenopausal BrCA	E2	9	2365	42	1.29 (1.14–1.45)	72	227	NA	1.26 (1.07–1.49)	27	NA

IGF, insulin-like growth factor; CRC, colorectal cancer; IGFBP, insulin-like growth factor binding protein; CA, cancer; BrCA, breast cancer; PrCA, prostate cancer; ESCC, esophageal squamous cell carcinoma; T, testosterone; E2, estradiol; DHT, dihydrotestosterone; A-diol G, androstanediol glucuronide; DHEA-S, dehydroepiandrosterone sulfate; D4, androstenedione; SHBG, sex hormone binding globulin; E1, estrone; SFA, total saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; *H. pylori*, *Helicobacter pylori*; HPV, human papillomavirus; HBV, hepatitis B virus; HCV, hepatitis C virus; *T. vaginalis*, *Trichomonas vaginalis*; DDT, dichlorodiphenyltrichloroethane; Cur, current; For, former; Nev, never; NA, non-statistically significant meta-analyses not applicable to the FSN, and statistically significant meta-analyses not applicable to the conditional power analysis.

1. Rosenberg's FSN – the number of future studies averaging null effect and average weight to reduce the summary OR to null

2. Orwin's FSN – the number of future studies averaging null effect to reduce the summary OR to 1.05

3. Number of future studies of average weight and no between-study heterogeneity needed to be included in the updated meta-analysis to achieve 80% power to detect the observed fixed-effect summary OR

4. Number of future studies of average weight and average between-study heterogeneity need to be included in the updated meta-analysis to achieve 80% power to detect the observed random-effects summary OR

Table 2.

Results of conditional power for 9 meta-analyses of circulating androgens concentrations and prostate cancer risk

Comparison	No. included studies	No. cases & controls	I^2	Fixed-effect[1]			Random-effects[1]		
				Odds ratio	95% CI	Future studies[2]	Odds ratio	95% CI	Future studies[3]
SHBG	15	9702	0	0.86	0.76 – 0.97	1	0.86	0.76 – 0.97	1
Free T	14	9365	0	1.12	0.98 – 1.27	18	1.12	0.98 – 1.27	20
DHT	7	2455	0	0.88	0.69 – 1.11	41	0.88	0.69 – 1.11	80
E2	9	5225	0	0.92	0.78 – 1.09	62	0.92	0.78 – 1.09	162
T	17	10324	0	0.98	0.87 – 1.10	502	0.98	0.87 – 1.10	3602
D4	6	4211	0	1.02	0.85 – 1.21	994	1.02	0.85 – 1.21	3995
Free E2	8	4778	0	0.97	0.82 – 1.16	1173	0.97	0.82 – 1.16	5279
DHEA-S	7	3024	17	1.22	0.98 – 1.53	8	1.29	0.99 – 1.68	5
A-diol G	8	5488	24	1.12	0.96 – 1.31	17	1.15	0.95 – 1.38	28

T, testosterone; E2, estradiol; DHT, dihydrotestosterone; A-diol G, androstanediol glucuronide; DHEA-S, dehydroepiandrosterone sulfate; D4, androstenedione; SHBG, sex hormone binding globulin.

1. Fixed-effect and random-effects estimates reported by Tsilidis et al. (7) calculated from study-specific estimates for individual components in the androgen pathway and prostate cancer from Roddam et al. (43)

2. Number of future studies of average weight as studies included in observed meta-analysis needed to achieve 80% in updated meta-analysis determined by conditional power assuming no between-study heterogeneity

3. Number of future studies of average weight and equivalent between-study heterogeneity as studies included in observed meta-analysis needed to achieve 80% power in updated meta-analysis determined by conditional power assuming equivalent between-study heterogeneity in updated meta-analysis