

Metabolic Syndrome and Risk of Cancer

A systematic review and meta-analysis

KATHERINE ESPOSITO, MD, PHD¹
PAOLO CHIODINI, PHD²
ANNAMARIA COLAO, MD³

ANDREA LENZI, MD⁴
DARIO GIUGLIANO, MD, PHD⁵

OBJECTIVE—Available evidence supports the emerging hypothesis that metabolic syndrome may be associated with the risk of some common cancers. We did a systematic review and meta-analysis to assess the association between metabolic syndrome and risk of cancer at different sites.

RESEARCH DESIGN AND METHODS—We conducted an electronic search for articles published through October 2011 without restrictions and by reviewing reference lists from retrieved articles. Every included study was to report risk estimates with 95% CIs for the association between metabolic syndrome and cancer.

RESULTS—We analyzed 116 datasets from 43 articles, including 38,940 cases of cancer. In cohort studies in men, the presence of metabolic syndrome was associated with liver (relative risk 1.43, $P < 0.0001$), colorectal (1.25, $P < 0.001$), and bladder cancer (1.10, $P = 0.013$). In cohort studies in women, the presence of metabolic syndrome was associated with endometrial (1.61, $P = 0.001$), pancreatic (1.58, $P < 0.0001$), breast postmenopausal (1.56, $P = 0.017$), rectal (1.52, $P = 0.005$), and colorectal (1.34, $P = 0.006$) cancers. Associations with metabolic syndrome were stronger in women than in men for pancreatic ($P = 0.01$) and rectal ($P = 0.01$) cancers. Associations were different between ethnic groups: we recorded stronger associations in Asia populations for liver cancer ($P = 0.002$), in European populations for colorectal cancer in women ($P = 0.004$), and in U.S. populations (whites) for prostate cancer ($P = 0.001$).

CONCLUSIONS—Metabolic syndrome is associated with increased risk of common cancers; for some cancers, the risk differs between sexes, populations, and definitions of metabolic syndrome.

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The metabolic syndrome is a cluster of risk factors for cardiovascular disease and type 2 diabetes and constitutes a growing problem worldwide (1). These factors include obesity (particularly central adiposity), dysglycemia, raised blood pressure, elevated triglyceride levels, and low HDL cholesterol levels. On the basis of the most recent epidemiological analysis using the American Heart Association/National Heart, Lung, and Blood Institute 2005 guidelines, similar to those of National

Cholesterol Education Program/Adult Treatment Panel III, slightly more than one-third (35%) of adults in the U.S. could be characterized as having the metabolic syndrome (1). This translates to nearly 80 million U.S. adults affected by the syndrome (calculated from U.S. Bureau of the Census data for 2007, with an adult resident population of 228 million). A higher percentage (40.1%) of prevalence occurred with revised International Diabetes Federation 2005 criteria, which use a lower cutoff point for

waist (≥ 94 cm in men and ≥ 80 cm in women).

Available evidence from epidemiologic investigations and experimental, translational, and clinical studies supports the emerging hypothesis that metabolic syndrome may be an important etiologic factor for the development and progression of certain types of cancer and also for overall cancer mortality (2). Differences in the study populations, length of follow-up, sample sizes, frequency of events, study end points, and statistical adjustment for confounding may all have contributed to the conflicting patterns of association seen in earlier studies. Moreover, both obesity (3) and diabetes (4) have repeatedly been associated with increased incidence for some common cancers, and both conditions represent two important factors contributing to the prevalence of the metabolic syndrome. There is also some evidence that dyslipidemia (low HDL cholesterol levels and/or raised triglyceride) is associated with some cancers (5). It therefore remains possible that some of the associations between metabolic syndrome and cancer risk may be mediated by the coexistence of obesity and overt diabetes.

A systematic and quantitative assessment of published studies is not available. Therefore, we conducted a meta-analysis to summarize all published studies to date on the incidence of cancer associated with metabolic syndrome.

RESEARCH DESIGN AND METHODS

Data sources

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist for reporting systematic reviews and meta-analyses (6). We systematically searched Medline, Embase, CENTRAL, CINAHL, and Web of Science through October 2011 for studies in humans of the association between metabolic syndrome and cancer. Our core search consisted of the terms metabolic syndrome, insulin resistance syndrome, and syndrome X, combined with specific terms for each cancer site: colorectal (colon and rectum), gastric, esophageal,

From the ¹Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, Naples, Italy; the ²Department of Medicine and Public Health, Second University of Naples, Naples, Italy; the ³Section of Endocrinology, Department of Molecular and Clinical Endocrinology and Oncology, University of Naples "Federico II," Naples, Italy; the ⁴Department of Experimental Medicine, University of Rome "La Sapienza," Rome, Italy; and the ⁵Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples, Italy.

Corresponding author: Dario Giugliano, dario.giugliano@unina2.it.

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Table 1—Baseline characteristics of studies included in meta-analysis

Cancer sites	No. of datasets*	Population group				No. of cases in men	No. of cases in women	MS: traditional vs. non-traditional§	Type of studies
		U.S.	Europe	Asia	Other				
Colorectal	38	6	23	9		6,661	4,341	14 vs. 8	9 cohorts, 2 n-c/c, 1 RCT, 2 c/c
Colon	11		7	4		1,529	1,035		
Rectum	11		7	4		1,035	647		
Breast cancer	12	1	7	3	1, Brazil		9,643	5 vs. 4	4 cohorts, 1 RCT, 2 n-c/c, 2 c/c
Postmenopausal	7	1	4	2			5,161		
Hepatobiliary	14	3	5	6		Total 5,580 M and F		5 vs. 5	5 cohorts, 2 c/c
Liver	10	3	3	4		3,199	1,758		
Gallbladder	4		2			54	10		
				2		559 M and F			
Prostate	14	4	8	2		4,623		6 vs. 5	10 cohorts, 1 n-c/c, 2 c/c, 1 series
Endometrium	5		4		1, Canada		2,190		2 cohorts, 1 n-c/c, 2 c/c
Pancreas	9	1	6	2		823	527	3 vs. 6	4 cohorts, 1 c/c
Gastric	7	1	2	4		506	309		4 cohorts
Lung	7	1	2	4		536	174		4 cohorts
Bladder	4		4			1641	337		4 cohorts
Thyroid	4		4			137	258		4 cohorts
Ovary	2		2				654		2 cohorts
Total	116	17	67	30	2	18,180†	20,010†		

c/c, case-control; MS, metabolic syndrome; n-c/c, nested case-control; RCT, randomized controlled trial; traditional, diagnosis of MS made according to national and international scientific associations. M, male. F, female. *Datasets refers to a site-specific group per article. Several articles reported multiple sites: each site counted as one dataset; if an article reported separated analysis for sex or age at the same site, these were counted as two datasets. §Analysis was performed for cohorts only when numbers of datasets were nine or more. †Total *n* (both sexes) = 38,381 cases, to which must be added 559 cases for gallbladder cancer in both sexes (*n* = 38,940 cases).

hepatobiliary (liver and gallbladder), pancreas, lung, bladder, thyroid, renal, leukemia, malignant melanoma, multiple myeloma, and non-Hodgkin lymphoma for both sexes and prostate, breast, ovary, and endometrium for single sex. Relevant journals, bibliographies, reviews, and personal files were hand searched for additional articles. The search had no language restriction. The last search was performed on 31 October 2011. The electronic database search strategy for Medline is available in Supplementary Table 1.

Study selection

We included studies if 1) their aim was to assess the effect of metabolic syndrome on risk of cancer or association with cancer, 2) they reported the definition of metabolic syndrome according to criteria of national or international scientific associations, federations, or organizations (traditional definitions) or if they used proxy indicators in the absence of the original data (nontraditional definitions), and 3) they included at least three factors, even in the absence of others. We included cohort

studies, nested case-control studies, control arms from clinical trials, case-control studies, patient series, and mortality studies. We specified that every study must either report risk estimates (relative risks [RRs], odds ratios, hazard ratios, and standardized incidence ratio) with 95% CIs separately for men, women, or both or must report sufficient data to estimate these. If a site-specific dataset had been published more than once, we used the most recent publication. We included a specific cancer site in the analysis if there were at least two cohort datasets. We excluded studies that were not published as full reports, such as conference abstracts and letters to editors, and studies of cancer precursors (e.g., colorectal adenoma).

Data extraction

From each retrieved article, we extracted the following data: name of the first author, year of publication, country where the study was performed, specific outcomes, follow-up time, proportion of men and women, total number of individuals, number of cases, and risk estimates and their 95% CIs (presence versus

absence of metabolic syndrome). We collected data for the most adjusted model. Populations were categorized into four groups: U.S., Europe, Asia, and other. Returned articles were reviewed against inclusion and exclusion criteria by three reviewers (D.G., K.E., and P.C.) until interrater reliability ($\kappa \geq 0.60$) was established. Methodological quality of each study was assessed according to three study components that might affect the strength of the association between metabolic syndrome and cancer risk: length of follow-up for cohort studies, whether metabolic syndrome definition was traditional or nontraditional, and the extent of adjustments for potential confounding factors. We also collected, where available, risk estimates of the association with cancer for each single factor of the syndrome taken at its highest level.

Data synthesis and analysis

The primary end point was to assess the association between metabolic syndrome and cancer risk in cohort studies. For the main outcome at each cancer site, we graded the evidence for study quality and

for the risk of bias: study quality was based on the number of datasets, number of events, width of CIs, and heterogeneity; risk of bias was mainly based on type of study and adjustment for confounders. Unless otherwise stated, we used the most adjusted risk estimate from each study. Heterogeneity of the effect across studies was assessed by Q^2 statistics, which is distributed as χ^2 statistics (7). A value of $P < 0.10$ was used to indicate lack of homogeneity (heterogeneity) among effects. I^2 statistics were provided to quantify the percentage of total variation across studies that was attributable to heterogeneity rather than to chance. I^2 values of 25, 50, and 75% correspond to cutoff points for low, moderate, and high degrees of heterogeneity. We used a fixed-effects model if I^2 value significance was >0.1 ; otherwise, we used a random-effect model. We did subgroup analyses for each site to identify study-level factors that modify the association between the presence of metabolic syndrome and cancer risk: these factors include sex, subsite (e.g., colon and rectum), definition of metabolic syndrome (traditional versus nontraditional), and design; for incidence of cancer, we considered cohort studies, nested case-control studies, and control arms of clinical trials. Sensitivity analyses evaluated whether the results could have been affected markedly by a single study and were repeated using a fixed-effects model. Publication bias was examined in funnel plots and with a regression asymmetry test: the Egger test is best for cancer sites with 10 or more datasets. We used STATA, version 9.0 (STATA, College Station, TX), to analyze data.

RESULTS—We screened 2,628 potentially relevant, nonduplicate articles. The κ score for concordance between reviewers rating the articles was 0.62–0.77. The final number of articles (8–50) included in the meta-analysis was 43 (Supplementary Fig. 1), which reported on 116 datasets (Supplementary Table 2). All articles were published in English. The characteristics of included studies are summarized in Table 1 and Supplementary Table 3. The analysis included 38,940 cancer cases (18,180 men and 20,201 women, plus 559 cases for gallbladder cancer not divided by sex). The median follow-up per cohort studies and per cancer site varied from 3 years (endometrium) to 12.2 years (prostate). Notably, no North American population data contributed to the summaries for gallbladder, ovary, thyroid,

and bladder cancers. The proportion of studies in which the definition of metabolic syndrome was traditional varied by cancer sites: higher for colorectal (14 vs. 8 nontraditional); approximately equal for breast, hepatobiliary and prostate; and lower for pancreas. No further differentiation was made when the number of datasets for cancer site was four or fewer. The number of potential confounding factors

(cancer-site-specific risk factors) included in the adjusted analyses also varied (Supplementary Table 3).

Fig. 1A and B shows the results of meta-analyses of RR (for presence of metabolic syndrome) in men and in women, respectively, for cohort studies only. Separate meta-analyses for some relevant sites and for sex are given in Supplementary Figs. 1–6. In men, the presence of metabolic

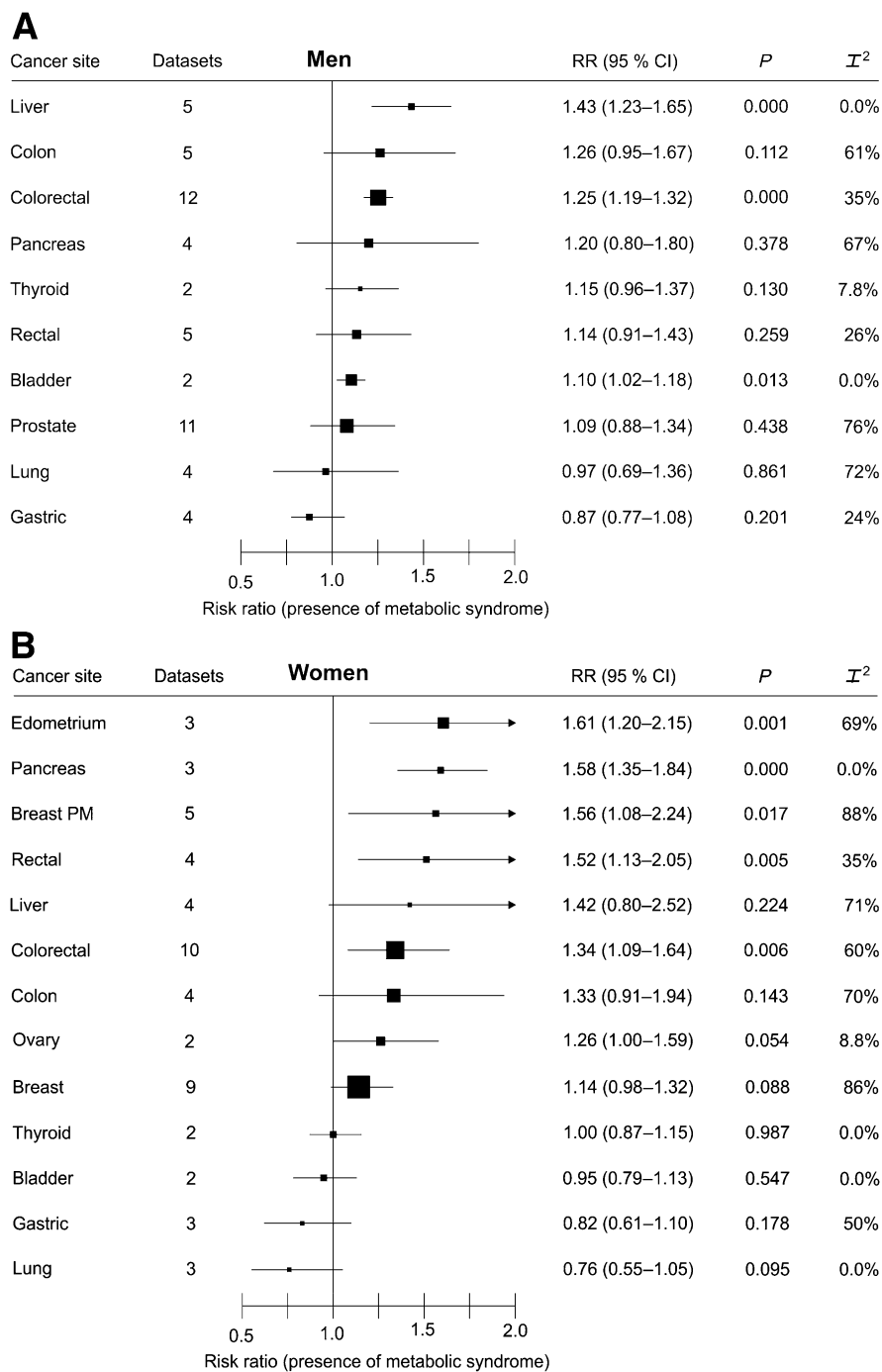


Figure 1—Summary risk estimates by cancer sites in men (A) and in women (B).

syndrome was associated with liver (Fig. 2; RR 1.43, $P < 0.0001$) and colorectal (Fig. 2A; 1.25, $P < 0.001$) cancers and weakly associated with bladder cancer (1.10, $P = 0.013$). Between-study heterogeneity was low or moderate for liver, colorectal, and bladder cancer ($I^2 = 0.0$, 35, and 0.0%, respectively) (Fig. 1A). The quality of the evidence was high for the association with colorectal cancer (high number of datasets and events, narrow CIs, and low heterogeneity), moderate for liver cancer, and low for bladder cancer. The overall risk of bias was low, as all studies were

prospective cohort studies and most adjusted for many confounders.

In women, the presence of metabolic syndrome was associated with endometrial (Fig. 2B; RR 1.61, $P = 0.001$), pancreas (Fig. 2B; 1.58, $P < 0.0001$), breast postmenopausal (Fig. 2B; 1.56, $P = 0.017$), rectal (1.52, $P = 0.005$), and colorectal (Fig. 2B; 1.34, $P = 0.006$) cancers; the association with ovary cancer (1.26) was of borderline significance ($P = 0.054$). Between-study heterogeneity was high for endometrial, breast postmenopausal, and colorectal cancers and

moderate or low for rectal ($I^2 = 35\%$), pancreas (0.0%), and ovary cancers (8.8%) (Fig. 1B). The quality of the evidence was moderate for the association with colorectal and pancreas cancers and low for endometrium and breast postmenopausal cancers. The overall risk of bias was low, as all studies were prospective cohort studies and most adjusted for many confounders. Associations with metabolic syndrome were stronger in women than in men for pancreas ($P = 0.01$), rectal ($P = 0.01$), and bladder ($P = 0.01$) cancers.

We also examined whether estimates varied between populations in cancer sites for which we had at least two datasets from the main geographical regions (Table 2). For colorectal cancer, for example, we recorded a positive association in U.S. and Europe populations for men and in Europe populations for women; for postmenopausal breast cancer, the positive association was lost in Europe populations; for liver cancer, the association remained significant in Europe and Asia populations for men only; and for prostate cancer the association became negative in U.S. populations (almost exclusively whites, RR 0.79, $P = 0.001$, $I^2 = 9\%$). This last figure was also significant if a mortality study (dataset $n = 69$) was excluded (RR 0.75 [95% CI 0.60–0.94], $P = 0.011$, $I^2 = 0.0\%$).

We also examined mortality from cancer in the available studies for which we had at least two datasets (Table 2). There were three cohort studies from the U.S. (two for both sexes, one for men only) and a case-control study from China (both sexes) for colorectal cancer only (8,9,16,20). Risk estimate for cancer mortality was 1.61 ($P < 0.0001$), with no heterogeneity ($I^2 = 0.0\%$).

We also examined whether results for cancer association differed according to whether studies of different design (case-control and patient series) were included in the full analysis (Table 2). For breast cancer, the inclusion of two case-control studies (26,27) with 3,950 cases produced a significant overall association (11 datasets, 9,643 cases) of 1.23 ($P = 0.009$) with high heterogeneity (88%). For liver cancer, the inclusion of two large case-control studies (29,30), with an additional 4,951 cases, produced a significant association for women (RR 1.62, $P < 0.0001$).

The definitions used for diagnosis of metabolic syndrome affected estimates of the association between metabolic

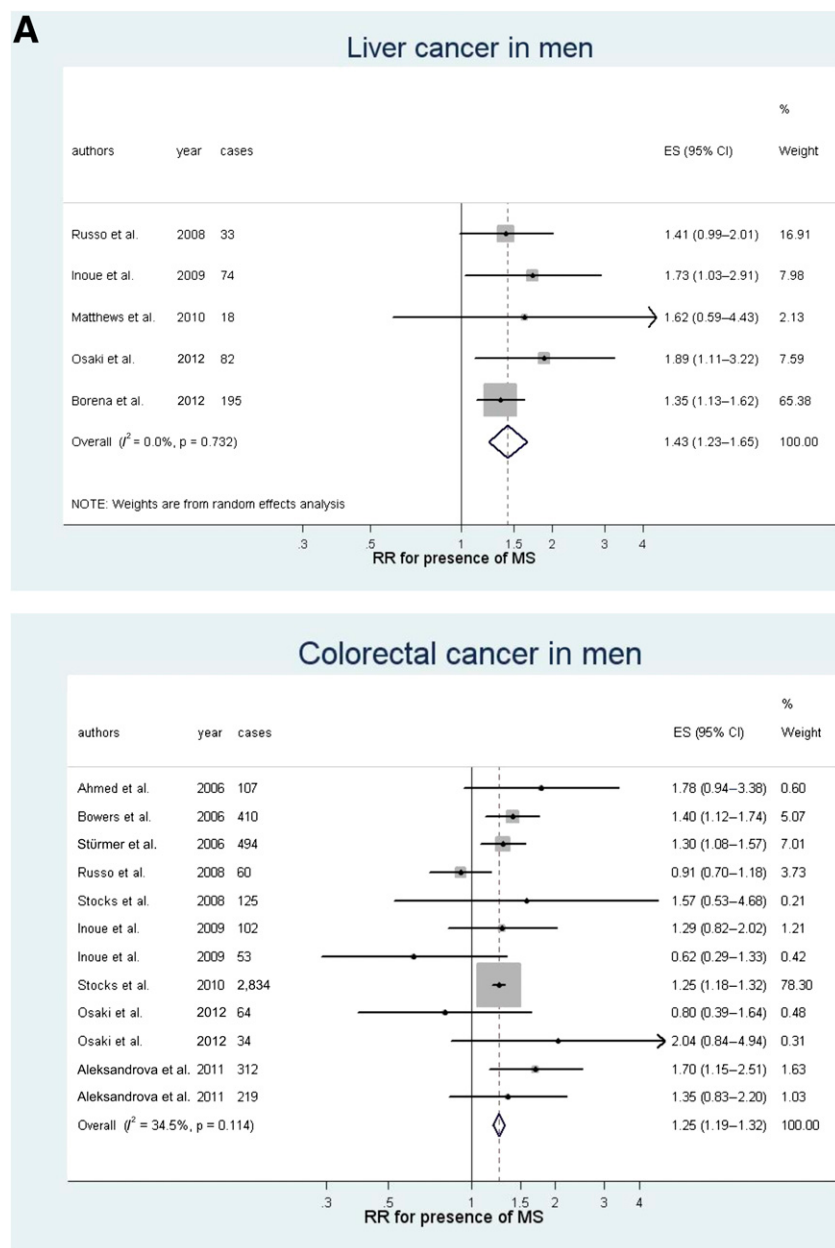


Figure 2—Meta-analyses for some common cancer sites in both sexes: colorectal and liver cancer in men (A) and colorectal, breast postmenopausal, endometrial, and pancreatic cancer in women (B). ES, effect size; MS, metabolic syndrome.

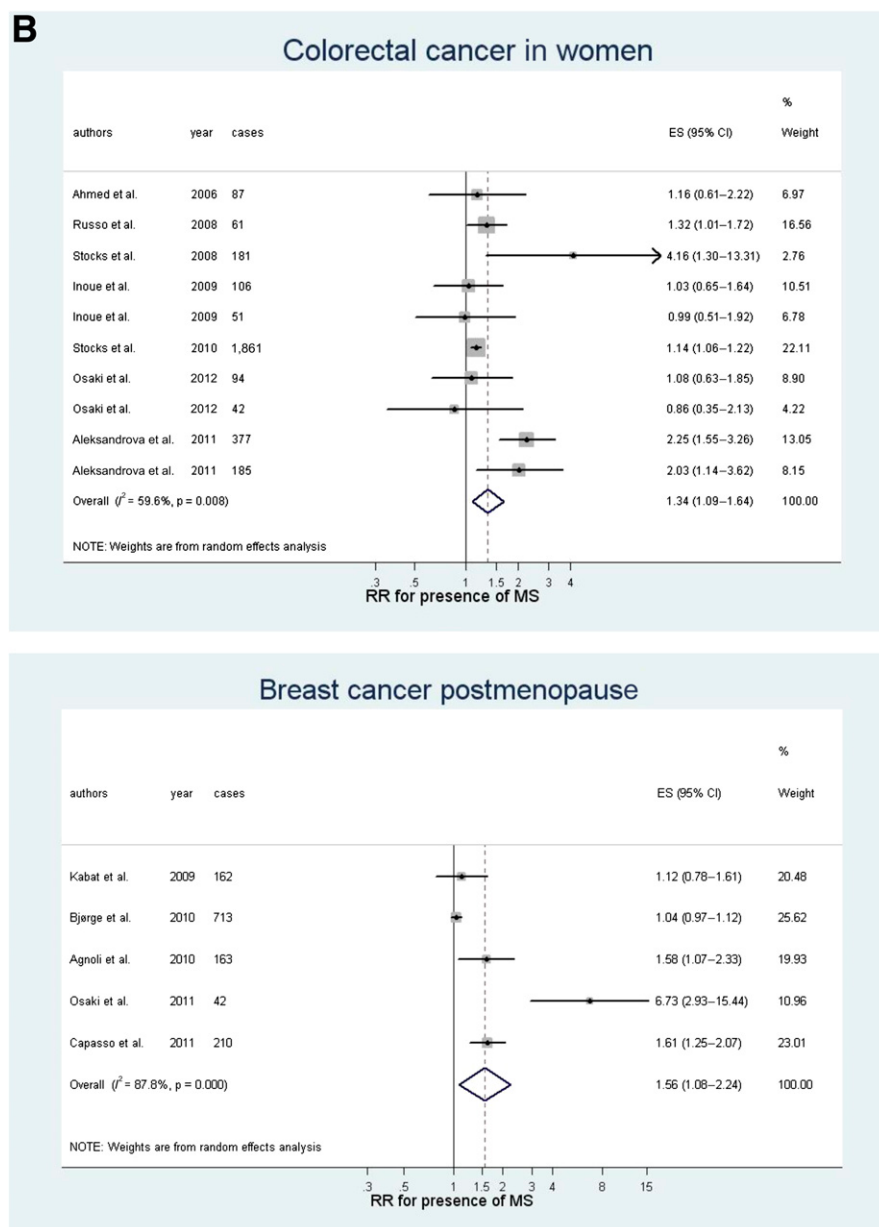


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syndrome and cancer risk (Table 2). For both sexes, the estimates remained similar for colorectal cancer (RR 1.33 and 1.22 for traditional versus nontraditional definitions); for liver cancer, both definitions achieved significant associations (1.88 and 1.51); for pancreas cancer, there was no association with traditional definitions (RR 1.13, $P = 0.745$); for prostate cancer, both definitions gave similar results; and for breast cancer, there was an association with traditional definitions only (1.45, $P = 0.025$).

To summarize the results for cohort studies with available data (32 cohorts), risk estimates for single factors were

equal to metabolic syndrome in 15 cohorts, higher in 11 cohorts, and lower in 6 cohorts. For colorectal cancer, for example, all increased cancer risk was explained by diabetes alone (9,10), diabetes and waist (10), diabetes and BMI (12), and triglycerides >150 mg/dL (15); other single or combined factors explained part (from 30 to 50%) of the increased risk conveyed by metabolic syndrome: BMI (11,21), waist (16,19), BMI and lipid (17), BMI and dysglycemia (14), and hypertension (21).

Influence analysis showed that no single study affected the sex-specific

summary estimates for most sites. Moreover, we did not note funnel plot asymmetry for cancer sites where a sufficient number of datasets existed to run the Egger test (colorectal cohorts men, $P = 0.912$; colorectal cohorts women, $P = 0.201$; and prostate cancer cohorts, $P = 0.085$).

CONCLUSIONS—Our results from meta-analyses of prospective cohort studies indicate that metabolic syndrome is consistently associated with an increased risk of several cancers in adults. However, many of the reported associations are small (RR between 1.1 and 1.6) and might differ between sexes for some sites and also across populations. In particular, the associations were stronger in women for some cancers (pancreas and rectal), and the magnitude of the associations was highest for sex-specific cancers (endometrial and breast postmenopausal). Moreover, from analyses in which sufficient datasets existed, the association was stronger for colorectal cancer in female European populations (RR 1.64 [95% CI 1.17–2.28]; five datasets with 2,665 incident cancers) and became protective for prostate cancer in the white U.S. populations, which needs confirmation from future studies. Given the widespread diffusion of metabolic syndrome (1) and the increased cancer mortality associated with metabolic syndrome (2), the findings of the present meta-analysis may have a clinical significance. At least for some common cancer sites (colorectal cancer in both sexes, liver cancer in men, and pancreas cancer in women), we are confident that the results are real, as the grading for study quality was moderate to high and overall risk of bias was low. Moreover, the inclusion of the few case-control studies did not change the overall estimates significantly. In general, the most robust association seems to be with colorectal cancer in both sexes and liver cancer in men. However, part of the association may be explained by the presence of obesity and overt hyperglycemia.

Mechanisms that link metabolic syndrome and cancer risk are not fully understood. Metabolic syndrome may be a surrogate marker for other cancer risk factors, such as decreased physical activity, consumption of high-calorie dense foods, high dietary fat intake, low fiber intake, and oxidative stress (1). Excess adiposity, in particular visceral obesity, results in a state of chronic systemic low-grade inflammation, attributed to

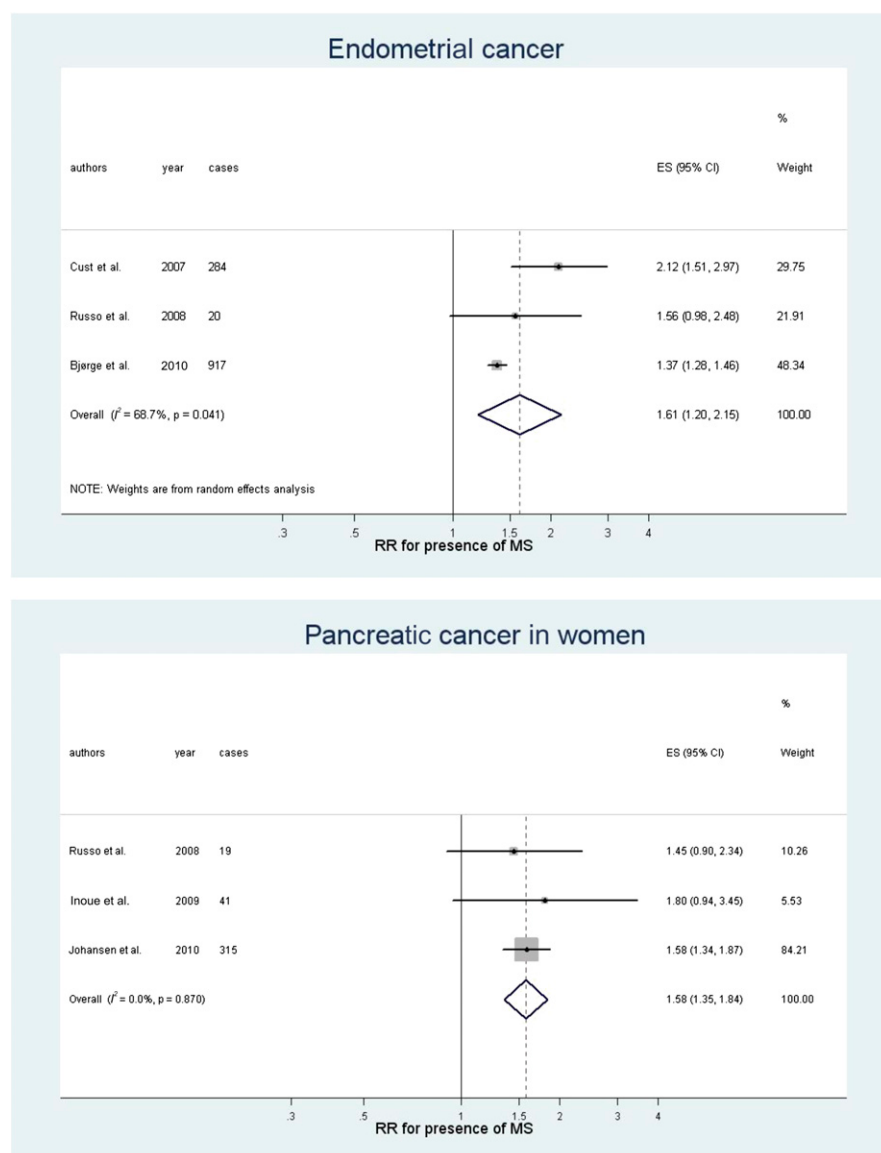


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production of inflammatory cytokines by both adipocytes and infiltrating immune cells creating a protumorigenic environment (51). By contrast, adiponectin levels are inversely associated with risk of some cancer, and some polymorphisms of adiponectin and its receptor genes are associated with multiple cancer risk (52). The altered balance between proinflammatory and antiinflammatory cytokines driven by central obesity might contribute to insulin resistance, a core component of the metabolic syndrome. The IGF-1 axis has also been implicated in the progression of breast, pancreatic, and esophageal cancer (53): levels of IGF are influenced by circulating insulin levels, with increasing insulin leading to decreased levels of IGF-binding proteins

1 and 2, thus increasing the bioavailability of IGF.

There were some limitations to this meta-analysis. Although not suggested by the formal statistical tests that we undertook, there is still a possibility of publication bias considering that the tests were likely to be underpowered. Moreover, we cannot exclude the possibility of residual confounding and bias because of misclassification. Although the included studies attempted to control for various known risk factors, the possibility of residual or unmeasured confounding cannot be ruled out. Single-point measurement increases the chance of random measurement error, which may underestimate the reported associations. Studies on the association between metabolic syndrome and cancer

risk used different factors and cutoff points, which complicate comparisons between studies. Additionally, metabolic factors were not directly measured in some cohorts but replaced either by proxy indicators of the factor (i.e., hypercholesterolemia as a proxy indicator of high triglyceride and/or low HDL cholesterol levels), self-reported diagnosis of diseases (i.e., diabetes, hypertension), or specific drug use (antidiabetic, antihypertensive, and antidyslipidemic). However, there was a consistent positive association between studies, despite the use of different definitions.

There were also strengths to this analysis. Our pooled estimates for the primary end point were based on prospective analyses with detailed adjustment for a wide range of variables. We used uniform methods and subgroup analyses to better define associations across cancer types between sexes, populations, cancer subsites, and definitions of metabolic syndrome. Moreover, this is the first meta-analysis that entailed a comprehensive search for all studies that assessed association between metabolic syndrome and cancer risk.

Findings from this meta-analysis, which includes many recently published studies, suggest that metabolic syndrome is associated with increased risk of common cancers. The excess risk of cancer conferred by metabolic syndrome is low to moderate and in part explained by accompanying obesity of hyperglycemia. Nevertheless, the increasing prevalence of metabolic syndrome worldwide and the high incidence of some malignancies, particularly colorectal and breast cancers, imply that every year many cases of cancer are attributable to metabolic syndrome. Preventive strategies (primary prevention and early detection of cancer) are urgently needed, as has been suggested for patients affected by fully developed diseases, such as diabetes (54). Moreover, patients with the metabolic syndrome, even in the absence of obesity or diabetes, should be encouraged to undergo appropriate cancer screenings, at least for some more frequently involved sites, as recommended for all people of their age and sex. More importantly, we need evidence of whether effective interventions to reduce the prevalence of metabolic syndrome in adult populations (55) will reduce cancer risk. The formulation of public health strategies based on sustained and bearable lifestyle changes can hopefully obtain significant results in the fight against cancer at the population level.

Table 2—Main analyses and prespecified subgroup analyses for cancer sites

Groups	Datasets	Identification of datasets (Supplementary Table 1)	Cases	RR (95% CI)	P	I ² (%)	P of I ²	Model
Colorectal	1–38							
Cohorts, men	12	5, 7, 10, 11, 17, 19, 21, 24, 26, 28, 30, 32	4,814	1.25 (1.19–1.32)	0.000	34.9	0.111	F
U.S.	2	5, 10	601	1.33 (1.11–1.59)	0.002	0.0	0.356	F
Europe	6	7, 11, 17, 24, 30, 32	3,960	1.26 (1.09–1.46)	0.002	47.7	0.089	R
Asia	4	19, 21, 26, 28	253	1.10 (0.80–1.51)	0.568	43	0.153	F
Cohorts, women	10	6, 12, 18, 20, 22, 25, 27, 29, 31, 33	3,045	1.34 (1.09–1.64)	0.006	59.6	0.008	R
U.S.	1	6	87	1.16 (0.60–2.20)				
Europe	5	12, 18, 25, 31, 33	2,665	1.64 (1.17–2.28)	0.004	81	0.000	R
Asia	4	20, 22, 27, 29	293	1.02 (0.76–1.36)	0.911	0.0	0.979	F
Mortality, men and women	6	1, 2, 3, 4, 23, 34	887	1.61 (1.28–2.01)	0.000	0.0	0.776	F
Colon men	6	8, 13, 19, 26, 30, 35	1,529	1.33 (1.02–1.73)	0.033	59.3	0.031	R
Colon women	5	14, 20, 27, 31, 36	1,035	1.29 (0.93–1.78)	0.128	62.3	0.031	R
Rectum men	6	9, 15, 21, 28, 32, 37	1,035	1.23 (1.00–1.52)	0.050	41.8	0.126	F
Rectum women	5	16, 22, 29, 33, 38	647	1.49 (1.13–1.97)	0.004	16.3	0.311	F
Traditional men and women	14	5, 6, 19, 20, 21, 22, 26, 27, 28, 29, 30, 31, 32, 33	1,833	1.33 (1.10–1.62)	0.004	40.7	0.057	R
Nontraditional men and women	8	7, 10, 11, 12, 17, 18, 24, 25	6,026	1.22 (1.18–1.34)	0.000	56.2	0.025	R
Breast	39–49							
All datasets	11	39–49	9,643	1.23 (1.05–1.45)	0.009	88	0.000	R
Cohorts	9	39–47	5,693	1.14 (0.98–1.32)	0.088	86	0.000	R
U.S.	1	40	162	1.12 (0.78–1.62)				
Europe	6	39, 42, 43, 44, 46, 47	5,334	1.09 (0.94–1.26)	0.258	88	0.000	R
Asia	2	41, 45	197	1.53 (0.45–5.21)	0.499	91	0.001	R
Cohorts, postmenopausal	5	40, 44, 45 ^a , 46, 47	1,290	1.56 (1.08–2.24)	0.017	88	0.000	R
U.S.	1	40	162	1.12 (0.78–1.62)				
Europe	3	44, 46, 47	1,086	1.35 (0.95–1.91)	0.094	86	0.001	R
Asia	1	45 ^a	42	6.73 (2.93–15.4)				
Case/control	2	48, 49	3,950	1.80 (1.43–2.27)	0.000	0.0	0.383	F
Traditional	5	40, 41, 45, 46, 47	732	1.45 (1.04–2.00)	0.025	71	0.008	R
Nontraditional	4	39, 42, 43, 44	2,961	0.97 (0.86–1.10)	0.633	84	0.000	R
Hepatobiliary	50–63							
Liver, all datasets, men and women	14	50–63	5,580	1.60 (1.32–1.94)	0.000	78.7	0.000	R
Liver, all datasets, men	7	50, 54, 56, 57, 59, 60, 61	3,199	1.65 (1.34–2.03)	0.000	79.5	0.000	R
Liver, all datasets, women	6	51, 55, 58, 59, 60, 61	1,758	1.62 (1.23–2.15)	0.000	86.5	0.000	R
Liver cohorts, men	5	50, 54, 56, 57, 59	402	1.43 (1.23–1.65)	0.000	0.0	0.732	F
U.S.	1	56	18	1.62 (0.59–4.41)				
Europe	2	50, 59	228	1.36 (1.16–1.60)	0.000	0.0	0.831	F
Asia	2	54, 57	156	1.81 (1.25–2.62)	0.002	0.0	0.816	F
Liver cohorts, women	4	51, 55, 58, 59	163	1.42 (0.80–2.52)	0.224	70.8	0.016	R
Europe	2	51, 59	76	1.01 (0.46–2.24)	0.973	64	0.095	R
Asia	2	55, 58	87	2.09 (0.69–6.37)	0.193	78	0.034	R
Traditional, men and women	5	54, 55, 56, 57, 58	261	1.88 (1.41–2.52)	0.000	18.5	0.297	F
Nontraditional, men and women	5	50, 51, 59, 60, 61	4,696	1.51 (1.16–1.98)	0.002	88.4	0.000	R

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Table 2—Continued

Groups	Datasets	Identification of datasets (Supplementary Table 1)	Cases	RR (95% CI)	P	I ² (%)	P of I ²	Model
Gallbladder and biliary, men and women	4	52, 53, 62, 63	623	1.53 (0.90–2.59)	0.113	81.3	0.000	R
Prostate	64–77							
All datasets	14	64–77	4,623	1.13 (0.94–1.37)	0.178	74.3	0.000	R
Cohorts	11	64–74	2,609	1.09 (0.88–1.34)	0.438	76	0.000	R
U.S.	3	66, 69, 72	625	0.79 (0.69–0.91)	0.001	9	0.333	F
Europe	6	64, 65, 67, 68, 71, 73	1,713	1.28 (0.89–1.87)	0.083	76.6	0.001	R
Asia	2	70, 74	271	0.98 (0.71–1.36)	0.932	52	0.149	F
Traditional	7	64, 66, 69, 70, 71, 73, 74	1,670	1.03 (0.82–1.29)	0.780	66.5	0.006	R
Nontraditional	4	65, 67, 68, 72	939	1.18 (0.75–1.87)	0.472	83	0.000	R
Endometrium	78–82							
All datasets	5	78–82	2,190	1.40 (1.32–1.49)	0.000	46.3	0.114	F
Cohorts	3	78–80	1,221	1.61 (1.20–2.15)	0.001	68.7	0.04	R
Pancreas	83–91							
All datasets, men	5	83, 85, 87, 89, 90	823	1.29 (0.88–1.89)	0.188	64.5	0.024	R
All datasets, women	4	84, 86, 88, 91	527	1.58 (1.35–1.84)	0.000	0.0	0.96	F
Cohorts, men	4	83, 85, 87, 89	649	1.20 (0.80–1.80)	0.378	67.2	0.027	R
Cohorts, women	3	84, 86, 88	375	1.58 (1.35–1.84)	0.000	0.0	0.870	F
Traditional, men and women	3	85, 86, 89	121	1.13 (0.53–2.43)	0.745	63	0.067	R
Nontraditional, men and women	6	83, 84, 87, 88, 90, 91	1,229	1.45 (1.12–1.87)	0.004	71	0.004	R
Gastric	92–98							
Cohorts, men	4	92, 94, 96, 97	506	0.87 (0.70–1.08)	0.201	24.8	0.232	F
Cohorts, women	3	93, 95, 98	309	0.82 (0.61–1.10)	0.178	50	0.135	F
Lung	99–105							
Cohorts, men	4	99, 101, 103, 104	536	0.97 (0.69–1.36)	0.861	72	0.013	R
Cohorts, women	3	100, 102, 105	174	0.76 (0.55–1.05)	0.095	0.0	0.436	F
Bladder	106–109							
Cohorts, men	2	106, 108	1,641	1.10 (1.02–1.18)	0.013	0.0	0.951	F
Cohorts, women	2	107, 109	337	0.95 (0.79–1.13)	0.547	0.0	0.903	F
Thyroid	110–113							
Cohorts, men	2	110, 112	137	1.15 (0.96–1.37)	0.130	7.8	0.298	F
Cohorts, women	2	111, 113	258	1.00 (0.87–1.15)	0.987	0.0	0.878	F
Ovary	114, 115							
Cohorts	2	114, 115	654	1.26 (1.0–1.59)	0.054	8.8	0.295	F

F, fixed; R, random.

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K.E. participated in the study conception and design; analyzed and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; had final approval of the manuscript; provided study materials; obtained funding; provided administrative, technical, or logistic support; and collected and assembled data. P.C. analyzed and interpreted data, critically revised the manuscript for important intellectual content, had final approval of the manuscript, and

provided statistical expertise. A.C. and A.L. analyzed and interpreted data, critically revised the manuscript for important intellectual content, and had final approval of the manuscript. D.G. participated in the study conception and design; analyzed and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; had final approval of the manuscript; provided study materials; provided statistical expertise; obtained funding; provided administrative, technical, or logistic support; and collected and assembled data. D.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the

integrity of the data and the accuracy of the data analysis.

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