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Association of Serum Immunoglobulin Levels with Solid Cancer: A Systematic Review and Meta-analysis



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ABSTRACT

Background: The nature of humoral immunity in carcinogenesis remains poorly understood. In this systematic review and metaanalysis, we aimed to evaluate the association of serum immunoglobulin classes with solid cancer and test our hypothesis that the immune escape of tumors is accompanied by dysregulated systemic immunoglobulin class-switching.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we systematically searched the Cochrane Library, Embase, and MEDLINE/PubMed databases for observational studies investigating the association between serum immunoglobulins (IgA, IgG, and IgM) and histologically confirmed diagnosis of solid cancer in adults. We selected case-control studies, including more than 20 cases, and those explicitly stating that no form of anticancer treatment was administered prior to immunoglobulin measurement. No eligible cohort studies were identified. The primary summary measure was the standardized mean differ-

Introduction

The ability of malignant cells to evade immune destruction has been established as a hallmark of cancer (1). During the last two decades, a plethora of experimental and clinical evidence has consolidated the central role of T cells in mediating cancer immunosurveillance and immunoediting and has led to the development of ground-breaking therapeutic interventions (2, 3). In contrast, the exact contribution of the B-cell compartment in cancer immunity remains poorly understood. The current body of evidence points toward a multifaceted role of different B-cell subsets, in which antibody-dependent and -independent mechanisms can both support and suppress carcinogenesis (4). ence (SMD) with 95% confidence intervals (CI) calculated using a random effects model.

Results: Pooling 11 eligible studies comparing serum IgA levels in 1,351 patients and 560 control subjects revealed a statistically significant SMD (1.50; 95% CI, 0.96–2.04). Nonsignificant SMDs were observed for the 14 selected studies investigating serum IgG [SMD, -0.02 (95% CI, -0.22 to 0.18)] and for the 10 studies reporting serum IgM [SMD, 0.11 (95% CI, -0.10 to 0.32)]. Substantial heterogeneity between studies was observed despite sensitivity analysis by immunoglobulin measurement method, control matching, type of cancer, stage of disease, and sequential study exclusion.

Conclusions: Serum immunoglobulin levels in patients diagnosed with solid cancer might be skewed toward class-switching to IgA, possibly reflecting Th2-polarized immunity.

Impact: Further combinatorial analyses of serum immunoglobulin isotypes alongside other immune parameters in databases and observational studies are warranted.

Animal studies investigating the effect of constitutive B-cell deficiency have supported a pivotal role of B cells in promoting tumor growth (5, 6). The production of potent immunosuppressive cytokines (e.g., IL10 and TGF β) and immune checkpoints (e.g., PD-L1) by regulatory B cells has been shown to suppress tumor-specific CD8⁺ T cells and induce the expansion of regulatory T cells, leading to immune tolerance against tumors (7–9). Furthermore, certain types of tumor-reactive antibodies can activate myeloid-derived suppressor cells (MDSC) to establish chronic inflammation in premalignant tissue (10), whereas antibodies from tumor-educated B cells can inhibit tumoricidal antibodies (11), as well as facilitate premetastatic niche formation in lymph nodes (12).

In parallel, the action of B cells also appears to be instrumental for multiple aspects of antitumor immunity. The presence of tumorinfiltrating B cells has been associated with improved outcomes in an increasing number of solid cancers (13). B cells can act as antigenpresenting cells in intratumoral tertiary lymphoid structures (TLS), where they can cross-present tumor antigens to cytotoxic CD8⁺ T cells (14), as well as provide secondary stimulation to CD4⁺ T cells (15). In TLS, B cells can undergo somatic hypermutation and class-switch recombination and differentiate into antibody-secreting plasma cells (16). The specific presence of tumor-infiltrating IgG⁺ plasma cells has been associated with favorable prognosis in many solid malignancies (17), including lung (18), ovarian (19), breast (20), and colorectal (21) cancers. In contrast, the expression of IgA or IgG4 by tumor-infiltrating plasma cells has been linked to poor outcomes in prostate cancer (22), pancreatic cancer (23), and melanoma (24, 25). In a recent animal study of hepatocellular carcinoma, IgA-producing plasma cells under the influence of TGF β were shown to be directly responsible for the transition of chronic inflammation to carcinogenesis via suppression of CD8⁺ cytotoxic T lymphocytes (26). The results of our work and those of others suggest that Th2 polarization of plasma

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cells, as manifested through a biased antibody class switching, may be associated with dysregulated immune responses in the context of cancer (16, 18, 25, 27).

In a previous systematic review and meta-analysis, we reported an inverse association between serum IgE levels and cancer risk (28). Given that B cells are exquisite sensors and powerful modifiers of the tumor immune environment, the humoral immune system appears to be ideally positioned to reflect the cancer immune-set point: the product of multiple host, tumor, and environmental factors that may determine the ultimate outcome of immunity against tumors in an individual (29). In the present study, we aimed to summarize the evidence for the association of the major serum immunoglobulin (IgA, IgG, and IgM) levels with solid cancer in adults and test our hypothesis that a skewed immunoglobulin class switching at the systemic level accompanies the immune escape of incipient tumors.

Materials and Methods

Search criteria

The present systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (30). The study methodology, including the search strategy, inclusion and exclusion criteria and the plan for meta-analysis, was finalized prior to conducting the review. The review protocol has not been previously registered or published online. Further details about the study, including the PRISMA checklist, the search strategy and results from each individual database search and a list of excluded studies, can be found in Supplementary Tables S1–S3 (available online).

Study selection

The aim of our search was to identify all observational studies investigating the association between serum immunoglobulin levels and solid cancer, published to date. The following inclusion criteria were used according to the population, intervention/exposure, comparator, outcome, and study design approach.

Population

Only studies with adult participants were included, as serum immunoglobulin levels can vary significantly between birth and adulthood (31). Studies in which participants had any diagnosed comorbidities (e.g., chronic infection or inflammatory disease) were excluded, as these could potentially affect serum immunoglobulin levels. The study protocol should explicitly state that cases had not received any form of anticancer treatment prior to baseline serum immunoglobulin measurement.

Exposure

A solid cancer diagnosis confirmed by histopathology. Studies on hematological malignancies were not assessed, as abnormalities in serum immunoglobulin levels could be causally related to immune paresis or paraprotein production (32).

Comparator

Adult healthy controls.

Outcome

Total serum immunoglobulin (IgA, IgG, or IgM) levels measured by any laboratory method. Studies reporting serum immunoglobulin subclass (e.g., IgG1, IgG2, etc.) levels were only included if the total level for that immunoglobulin class was also reported.

Study design

An observational study (case-control or cohort study), including more than 20 cases. Case reports and case series were excluded.

Data sources

Our search included all records listed in the following computerized literature databases since their inception: the Cochrane Library, Embase/Embase Classic and MEDLINE (up to March 31, 2018) and Pubmed/MEDLINE (up to July 22, 2018). In order to maximize the sensitivity of our search, we did not use any preset search filters or language restrictions. Studies not written in English were translated using commercially available software. Gray literature in the form of conference abstracts was also included, as long as sufficient information regarding the study methodology and results was available.

The detailed search strategy for each individual database is provided in Supplementary Table S2. We searched the Cochrane Library using the free-text term "cancer" or the Medical Subject Headings (MeSH) term "neoplasms" combined with the MeSH terms "Immunoglobulin A," "Immunoglobulin G," or "Immunoglobulin M." For the Embase/ Embase Classic and MEDLINE databases, we searched study titles, abstracts, and author keywords using the free-text term "cancer" or the EMTREE term "malignant neoplasm" combined with the EMTREE terms "immunoglobulin A," "immunoglobulin G," or "immunoglobulin M." Finally, we searched titles and abstracts listed in the Pubmed/ MEDLINE database using the terms "cancer" or "neoplasm" combined with the terms "immunoglobulin A" or "serum IgA," "immunoglobulin G" or "serum IgG," and "immunoglobulin M" or "serum IgM." The reference lists of all assessed full texts were also manually screened, and additional, potentially eligible studies were evaluated based on the aforementioned inclusion criteria (Supplementary Fig. S2).

Data extraction

The titles and abstracts of all identified records from each database search were imported to the commercial reference management software Endnote (Clarivate Analytics), which facilitated the identification and removal of duplicate records. Each identified duplicate record was manually checked prior to removal. Following screening of the titles and abstracts of all imported records, two investigators (I. Peppas and S. Sollie) independently assessed the full texts of potentially eligible studies with almost perfect agreement (91.97% agreement, Cohen's kappa 0.809) and performed data extraction. In cases of disagreement, consensus was reached following input from a third investigator (M. Van Hemelrijck), resulting in genuine consensus among all three investigators. No eligible cohort studies were identified. The final list of selected case–control studies was approved by all authors.

For each selected study, the following data were extracted into an *a priori* designed data sheet: name of the first author, the year of publication, the country where the study was conducted, the type of study, the type of solid cancer and method of diagnosis, the number of cases and controls, the mean serum immunoglobulin levels and standard deviation for each group, and the method of immunoglobulin measurement. Information on the method of control selection, the age distribution, and the gender ratio of study groups was also extracted, when available.

Quality assessment

The methodological quality of selected studies was analyzed using the Newcastle-Ottawa Scale (NOS). The NOS for case–control studies is a nine-star scoring system used to assess their quality by focusing specifically on the reported methods of participant selection, study group comparability, and measurement of exposures and outcome (33). The NOS was customized to the review question of interest in order to account for the fact that all studies included healthy controls. Thus, the method of ascertaining immunoglobulin levels was used as a measure of methodological quality. Studies with a score of 6 stars or above were considered of good methodological quality (Supplementary Table S4).

Summary measures and statistical analysis

The principal measure of interest for selected studies was the mean serum immunoglobulin level and standard deviation for solid cancer cases and healthy control subjects. For studies in which the mean values were reported according to gender or stage of disease, amalgamation was performed by calculating the combined mean and standard deviation for the total number of cases and the total number of controls. Standard deviation was derived from the SEM, when only the latter was reported. All serum immunoglobulin levels were converted to mg/dL to facilitate comparison between studies.

The primary summary measure used in the meta-analysis was the standardized mean difference (SMD) in serum immunoglobulin levels between solid cancer cases and control subjects. The SMDs with 95% confidence intervals (CI) were calculated using a random effects model to allow for differences in the method and specific assay used for measuring serum immunoglobulin levels between studies. The SMDs were graphically presented in a forest plot for each immunoglobulin isotype (IgA, IgG, and IgM).

Potential heterogeneity between studies was assessed using the forest plots, as well as the I^2 Statistic (34). We additionally performed prespecified sensitivity analyses in terms of method of immunoglobulin measurement, study-by-study exclusion, and the type of solid cancer. Additional subgroup sensitivity analyses were conducted for gender-matched studies and according to the stage of cancer for all studies including relevant data. Potential publication bias was assessed using Funnel plots, as well as the Egger's test for small study effects by

performing regression of the normal deviate of the effect size against its standard error. A P value < 0.05 was considered statistically significant for publication bias. All statistical analyses were performed using STATA (version 15).

Results

Characteristics of selected studies

The PRISMA flowcharts for study selection, categorized by immunoglobulin isotype, are presented in Supplementary Fig. S1. All observational studies selected for analysis were casecontrol studies, as no eligible cohort studies were identified through our database search. Serum immunoglobulin levels were determined by six different methods. Earlier studies (35-40) used the radial immunodiffusion technique, which has been largely superseded by turbidimetry (41-43) and nephelometry (44, 45). Other techniques used included affinity chromatography (46-48) and enzyme-linked immunosorbent assay (49). Most studies (11 of 15) compared serum immunoglobulin levels of patients with cancer with age-matched control subjects, whereas matching of controls by gender was reported only in 9 studies. Among the 15 studies included, the most commonly investigated malignancy was head and neck cancer (8), followed by gynecological (3), breast (2), lung (1), and gastric (1) cancers. Vijavakumar and colleagues investigated serum immunoglobulin levels in three different types of solid cancer using a single group of 100 healthy control subjects for comparison (40).

All studies included in the current systematic review and metaanalysis were given a score of 6 or above in the NOS (Supplementary Table S4). The Egger's test was not suggestive of any significant publication bias (P > 0.30, **Figs. 1–3**).

Serum immunoglobulin A

7.82

6.62

7 96

7.54

7.39

7.96

7.91

7.98

8.01

7 90

7.45

7.67

7.79

100.00

The initial search of all databases for observational studies investigating the association of serum IgA with solid cancer

Egger test for small-study effects: P = 0.377

Funnel plot with pseudo 95% confidence limits

SMD



Study

Plesničar, 1972 (35); uterir

lly, 1982 (36); head and ne

ux 1982 (37): breast

nna, 1982 (38); head and neck

umar, 1986 (40): head and ne

ar, 1986 (40); uterin

nar, 1986 (40); breas

1986 (44); head and nee

ntz, 1988 (42); head and necl

Schantz, 1989 (41); head and neck de Souza, 2003 (45); head and nec

Overall (I-squared = 96.3%, P = 0.000)

Sadat, 2008 (43); lung

Forest plot for studies comparing mean serum IgA levels in patients with solid cancer and healthy adult controls with associated funnel plot and Egger test for small-study effects.

SMD (95% CI)

0.42 (0.03-0.81)

3.79 (2.88-4.70)

0 54 (0 25-0 83)

2.79 (2.25-3.33)

3.33 (2.72-3.94)

2.05 (1.76-2.35)

2.66 (2.32-2.99)

1.49 (1.21-1.77)

1.06 (0.81-1.31)

0.43 (0.09-0.77)

1.25 (0.67-1.83)

-0.19 (-0.66 to 0.29)

0.34 (-0.07 to 0.75)

1.50 (0.96-2.04)

revealed a total of 476 citations. The characteristics of the 11 studies selected for analysis, which included a total of 1,351 cancer cases and 560 controls, are summarized in **Table 1**. Quantitative synthesis using a random effects model (**Fig. 1**) showed a pooled SMD of 1.50 (95% CI, 0.96–2.04). Subgroup analysis by type of solid tumor revealed significant SMDs for head and neck (1.77, 95% CI, 1.00–2.55), breast (1.02, 95% CI, 0.08–1.95), and lung cancer (0.34, 95% CI, 0.07–0.75; Supplementary Table S5). The pooled SMD from two studies on uterine cancer was 1.52 (95% CI, -0.65 to 3.73). We detected substantial heterogeneity between studies ($I^2 = 96.3\%$, P = 0.000). An I^2 statistic greater than 95% persisted despite sequential sensitivity analysis, in which one study was excluded each time, confirming that no single study was solely responsible for the observed heterogeneity.

Sensitivity analysis by method of immunoglobulin measurement and type of solid cancer did not substantially alter heterogeneity (Supplementary Table S5). Additional analysis performed by only including studies that used gender-matched controls yielded an SMD of 1.26 (95% CI, 0.52–1.99) with a similarly large heterogeneity (I^2 95.7%, P = 0.000, Supplementary Fig. S3A). Given that five studies reported serum IgA levels according to stage of disease, additional subgroup analysis for early (Stage I–II) and advanced (Stage III–IV) cancer yielded a pooled SMD of 0.82 (95% CI, 0.51–1.12) and 1.86 (95% CI, 1.18–2.55), respectively. Heterogeneity in reported mean serum IgA levels was modestly reduced for early cancer (I^2 78.81%, P = 0.000), but not for patients with advanced disease (I^2 94.41%, P = 0.000, Supplementary Fig. S3B and S3C).

Serum immunoglobulin G

The database search for serum IgG revealed a total of 2,067 citations. The 14 eligible studies selected for analysis of serum IgG levels included a total of 1,745 solid cancer cases and 1,032 control subjects (**Table 2**). A meta-analysis of selected studies (**Fig. 2**) showed an SMD of -0.02 (95% CI, -0.22 to 0.18) with an associated I^2 statistic of 84.1% (P = 0.000). Sensitivity analysis by sequential study exclusion did not significantly reduce the observed heterogeneity, as I^2 remained >79.5% in all cases (P = 0.000, results not shown).

Consistency of SMDs was observed only among the three studies measuring IgG by affinity chromatography ($I^2 = 0.0\%$; P = 0.803), which supported an overall small effect size (pooled SMD -0.28, 95% CI, -0.44 to -0.13). Sensitivity analyses by other methods of immunoglobulin measurement, type of solid cancer (Supplementary Table S5), gender-matching of controls, or stage of disease (Supplementary Fig. S4) did not alter significantly the pooled estimate and had a minimal effect on heterogeneity.

Serum immunoglobulin M

The initial database search for studies investigating serum IgM in relation to solid cancer revealed 416 citations. Following in depth review, ten studies were selected for analysis (**Table 3**). Quantitative synthesis of results yielded an overall SMD of 0.11 (95% CI, -0.10 to 0.32), as shown in **Fig. 3**. A large degree of heterogeneity was detected (I^2 78.8%, P = 0.000), which reduced to a minimum I^2 of 62.3% (P = 0.000) following sequential sensitivity analysis with study-by-study exclusion (results not shown). Sensitivity analyses by method of immunoglobulin measurement, type of solid cancer (Supplementary Table S5), stage of cancer, or selection of gender-matched studies (Supplementary Fig. S5) did not significantly alter the pooled estimate or improve heterogeneity.

Discussion

To our knowledge, this is the first systematic review and metaanalysis investigating total serum IgA, IgG, and IgM levels in patients with solid tumors and healthy adult control subjects. The scope of the present study was to investigate serum immunoglobulin levels in previously untreated patients with solid cancer in order to eliminate the potential confounding effects of surgery, chemotherapy, and radiotherapy. The 15 studies selected for analysis included a total of 1,066 healthy adult control subjects and 1,779 cases of a histopathologically confirmed solid cancer diagnosis in the absence of other known comorbidities.

The present meta-analysis revealed significantly higher serum IgA levels in patients with solid malignancies compared with healthy individuals, indicating an association of serum IgA class-switching with solid cancer diagnosis. The strength of this association persisted following subgroup analysis to account for differences in study meth-odology, type of solid cancer, and gender-matching of controls. Interestingly, a 2-fold increase in the SMD of IgA levels was found in advanced cancer compared with early cancer (Supplementary Fig. S3), further supporting the possibility that serum IgA levels may correlate with immune escape and tumor burden.

The association of a higher serum IgA level with worse prognosis in patients with cancer was reported by several studies included in the present systematic review, when patients were followed up after treatment. Vinzenz and colleagues reported that patients with head and neck cancer with disease relapse following treatment had significantly higher pretreatment serum IgA levels compared with patients without subsequent relapse (44). Vijayakumar and colleagues similarly reported that at 6 months after treatment, the serum IgA levels of patients who were clinically cured had reduced to normal values (40). In contrast, patients with residual lesions requiring ongoing chemotherapy showed persistently increased serum IgA levels. Schantz and colleagues reported an inverse association of pretreatment serum IgA with disease-free survival in patients with head and neck cancer (42), a finding that has also been supported by subsequent studies (50). These observations are also consistent with the results of a prospective cohort study in which high serum IgA associated with an increased mortality rate from solid cancer, but not with other common causes of death (51). The study did not investigate the relationship of serum IgA levels with cancer diagnosis.

Serum IgA normally accounts for about 15% of the total serum immunoglobulins (52). It is possible that a higher level of serum IgA could reflect a general propensity toward a Th2-biased immune response against tumors, which may be instructed by a combination of host, environmental, and tumor-specific factors. At the host level, increased serum IgA has been linked to older age, male gender, metabolic syndrome, and other well-known risk factors (52) associated with both immune dysregulation, cancer risk, and unfavorable prognosis. In addition, polymorphisms in cytokine genes could modify the threshold of immune tolerance to self, as evident by specific associations with the risk of either autoimmune conditions or cancer (53–55). In this context, polymorphisms in IL10, TGF β , and of other regulators of immunoglobulin production which support class switching to IgA may become important determinants of progression from cancer immunosurveillance to immune escape (56, 57).

Another possible role of IgA in tumor immunity arises from its dynamic relationship with environmental factors, such as diet and the microbiota. Disturbance of microbiome diversity was recently shown to influence multiple aspects of antitumor immunity, from modifying the risk of developing cancer (58, 59) to determining response to

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					Case	S			Control				
Study	Country	Method of IgA measurement	Types of cancer		Mean age (range), years	Mean serum IgA (SD), mg/dL	u	Mean age (range), years	Mean serum IgA (SD), mg/dL	Control selection	Matching	- J Association	c
Plesničar, 1972 (35)	Yugoslavia	RID	Uterine	17 i	54 (30-75,	195.1 (土43.3) ^{a,b}	38	36 (21-63)	175.0(土56.1) ^{a,b}	Blood	ι M	Positive	
					SD 11.8)					donors			
Scully, 1982 (36)	UK	RID	Head and neck	26 (J/S	379.0 (±38.0)	27	Age-matched	256.0 (土26.0)	U/S	GM AM	Positive	
Lamoureux, 1982 (37)	Canada	RID	Breast	196	54 (20-84)	274.0 (土168.0)	61	38 (20-47)	192.0 (土78.0)	U/S	۱ ع	Positive	
Khanna, 1982 (38)	India	RID	Head and neck	70	J/S (26-70)	358.7 (土79.2)	40	Age-matched	168.3 (土42.5)	U/S	– AM	Positive	
Rajendran, 1986 (39)	India	RID	Head and neck	20	46 (SD 10.1) ^a	327.5 (土41.4) ^b	50	37 (SD 6.7)	211.50 (±26.7) ^b	U/S	ן שט	Positive	
Vijayakumar, 1986 (40)	India	RID	Head and neck	196 4	48 (30-60) ^a	307.8 (土56.4)	100	36 ^a (20–50)	206.50 (±31.2)	Medical	I I	Positive	
			Uterine	172 4	44 (30-60) ^a	339.4 (土58.3)				campus		Positive	
			Breast	166 4	47 (30-60) ^a	284.3 (土61.2)				volunteers		Positive	
Vinzenz, 1986 (44)	Austria	Nephelometry	Head and neck	216 (J/S	346.4 (土166.3)	100	Age-matched	192.7 (土82.0)	U/S	GM AM	Positive	
Schantz, 1988 (41)	NSA	Immuno-turbidimetry	Head and neck	97	58 (27-82)	263.0 (土134.0)	53	59 (43-73)	212.0 (土85)	U/S	– AM	Positive	
Schantz, 1989 (42)	NSA	Immuno-turbidimetry	Head and neck	24 (J/S (20-40)	275.0 (土114.0)	32	U/S (20-40)	161.0 (土70.0)	U/S	– AM	Positive	
De Souza, 2003 (45)	Brazil	Nephelometry	Head and neck	34	55 (35-78)	279.40 (±137.7)	34	54 (32-75)	310.90 (土194.1)	U/S	GM AM	Negative	
Sadat, 2008 (43)	Bangladesh	Immuno-turbidimetry	Lung	45	52.3 (25-80,	506 (土188) ^c	50	52.9 (25-80,	450 (土140) ^c	U/S	GM AM	Positive	
					SD 12.0)			SD 13.2)					1
			Total	1,351			560						1
Abbreviations: AM, age-n ^a Amalgamation of values ^b SD calculated from SEM. ^c Values converted into m	natched; GM, g for each subg	lender-matched; RID, radia roup was required.	al immunodiffusion.	u/s, u	nspecified.								1

					Case	, a			Control				
	Country	Method of IgG measurement	Types of cancer	-	Mean age (range), years	Mean serum IgG (SD), mg/dL	- E	Mean age (range), years	Mean serum IgG (SD), mg/dL	Control selection	Matcl	jing	Association
Plesničar, 1972 (35)	Yugoslavia	RID	Uterine	77	54 (30-75, SD 118)	1,253.8 (±247.0) ^{a,b}	38	36 (21-63)	1,035.0 (±163.4) ^{a.b}	Blood	δ		Positive
Scully, 1982 (36)	СK	RID	Head and	26		1,449.0 (±559.0)	27	Age-matched	1,479.0 (±106.0)	U/S	Σ	MΑ	Negative
Lamoureux, 1982 (37)	Canada	RID	Breast	200	54 (20-84)	1,048.0 (±321.0)	118	38 (20-47)	1,153.0 (±310.0)	U/S	ъ	I	Negative
Khanna, 1982 (38)	n India	RID	Head and	70	U/S (26-70)	1,280.3 (±227.4)	40	Age-matched	1,361.0 (±233.7)	N/S	I	AΜ	Negative
Rajendran, 1986 / 201	India	RID	Head and	32	46 (SD 10.1) ^a	1,429.7 (土461.7) ^b	25	37 (SD 6.7)	1,495.4 (±422.7) ^b	U/S	δ	I	Negative
Vijayakumar,	India	RID	Head and	196	48 (30-60) ^a	1,489.7 (±411.3)	100	36 (20–50) ^a	1,521.4(土372.7)	Medical	Ι	I	Negative
			Uterine	172	44 (30-60) ^a	1,687.8 (±381.6)				volunteers			Positive
Vinzenz	Austria	Nenhelometrv	Breast Head and	166 223	47 (30-60) ^a 11/S	1,465.6(土421.4) 1194 3(+372 9)	5	Age-matched	1 091 6 (+252 2)	S/11	Σ	ΔM	Negative Positive
1986 (44)			neck				5	5		0.55	-	-	
Schantz,	NSA	Immuno-	Head and	97	58 (27-82)	1,010.0 (±293.0)	53	59 (43-73)	951.0(土217.0)	U/S	T	AΜ	Positive
1988 (41) Schantz	1ISA	turbidimetry Immino-	neck Head and	74	(07-067 S/11	1142 0 (+254 0)	22	(02-06) 2/11	0040743310	5/11	I	MA	Dositiva
1989 (42)	5	turbidimetry	neck				1			0.5		-	
Schauenstein, 1996 (46)	Austria	AC	Ovary and cervix	207	U/S (21-85)	960.0 (土431.6) ^{b.c}	135	Age-matched	1,090.0 (±232.3) ^{b,c}	N/S	Σ	MΑ	Negative
Schauenstein, 1997 (47)	Austria	AC	Colorectal	36	(S/N) 69	990.0 (±300.0) ^{b,c}	162	Age-matched	1,030.0 (土254.6) ^{b,c}	N/S	I	MΑ	Negative
Anderhuber, 1999 (48)	Austria	AC	Head and neck	74	N/S	960.0(土344.1) ^{b,c}	174	Age-matched	1,030 (±263.8) ^{b,c}	N/S	Σ	AΜ	Negative
Sadat, 2008 (43)	Bangladesh	n Immuno- turbidimetry	Lung	45	52 (20-80, SD 12.0)	1,496.0 (±392.0) ^c	50	45 (20-80, SD 13.2)	2,056 (土802) ^c	U/S	Σ	MΑ	Negative
Saito, 2017 (49)	Japan	ELISA	Gastric	100	N/S	9,05.1 (±412.2)	27	67 (SD 10.3)	1,037.0 (±293.3)	N/S	I	AΜ	Negative
			Total	1,745			1,032						
Abbreviations: AC, ^a Amalgamation of ^b SD calculated fror ^c Values converted	, affinity chrom values for eac. m SEM. into mg/dL.	natography; AM, age-r :h subgroup was requ.	matched; GM, ge ired.	:nder-m	atched; RID, radial i	mmunodiffusion; U/S, L	Inspeci	fie d.					

Table 2. Case-control studies selected for analysis of the association between serum IgG levels and different types of solid cancers.

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Figure 2.

Forest plot for studies comparing mean serum IgG levels in patients with solid cancer and healthy adult controls with associated funnel plot and Egger test for smallstudy effects.

immunotherapy (60, 61). A defining characteristic of IgA is the provision of mucosal immunity in the absence of inflammation (62). This is partly mediated by dimeric secretory IgA, which neutralizes antigens and prevents microbial adhesion to epithelial cells. IgA promotes bacterial symbiosis through protective opsonization, modification of their metabolism, and epitope expression (63), which may result in immune tolerance and the maintenance of gut microbiome diversity (64). Gut and lung microbiota are themselves capable of augmenting IgA class-switching through antigen presentation by CD103⁺ dendritic cells and induction of TGFβ and IL10 (65). CD103⁺ dendritic cells of the gut and skin are also able to induce T-cell anergy and Treg expansion by expressing aldehyde dehydrogenase and indoleamine 2,3-dioxygenase (66). In this context, tissue-specific immunoregulation may determine the ability of different tumors to exploit the IgA-microbiota axis in order to facilitate immune escape (67). More specifically, tissue-specific dendritic cells that are conditioned by the epithelial tissue environment to facilitate immune tolerance to commensal organisms (68) could be used by malignant cells of epithelial origin in order to precipitate a Th2-skewed immune response (69). Hughes and colleagues compared serum immunoglobulin levels in 256 control subjects and 984 patients with solid cancer (70). The study included participants less than 18 years old and did not specify whether patients had received any form of anticancer treatment prior to immunoglobulin measurement. However, the authors reported significantly increased levels of serum IgA in malignancies of epithelial tissues, which is in line with findings of the present study.

Additional important features of IgA include its failure to activate the complement system and the ability to mediate the regulatory effects of its main inducer, TGF β , through multiple mechanisms (71–73). In particular, monomeric IgA (accounting for 80%–90% of total serum IgA) exerts inhibitory effects on many immune cell subsets via activation of Fc α RI receptors (74, 75) and induction of IL10 production (76), as well as by directly inhibiting proinflammatory cytokines (77). Emerging evidence suggests that tumors can induce IgA class-switch recombination not only within the tumor microenvironment (22, 24–26), but also at the systemic level via dissemination of MDSCs. For example, the frequency of circulating CD11b⁺/CD16⁺ polymorphonuclear MDSCs correlates with poor survival in patients with head and neck cancer (78). In a murine animal model, CD11b⁺ MDSCs were found in close contact with B cells in the splenic germinal centers of tumor-bearing mice (79). Xu and colleagues showed that these MDSCs induced the differentiation of B cells into IgA-producing plasma cells via secretion of IL10 and TGF β . This observation has provided the first direct evidence supporting the association of tumor immune escape with systemic production of serum IgA.

IgG accounts for 75% of serum immunoglobulins and consists of 4 different subclasses (IgG1-IgG4; ref. 62). Although the present metaanalysis suggests a lack of association between total serum IgG levels and solid cancer, a lower IgG1/total IgG ratio has been reported in gynecological (46), colorectal (47), head and neck (48), and breast cancer (80). In contrast, a high serum IgG1/total IgG ratio is found in various autoimmune conditions such as systemic sclerosis, systemic lupus erythematosus, and primary biliary cirrhosis (81). On the other hand, a raised serum IgG4/Total IgG ratio has been reported in hepatocellular carcinoma (82) and melanoma (11) and has been associated with unfavorable disease prognosis. Increased serum IgG4 is also commonly found in a spectrum of fibroinflammatory conditions recently termed IgG4-related disease (IgG4RD), in which abnormal, yet reversible, collagen deposition gives rise to clinical and radiological characteristics that resemble malignancy (83). It is possible that a sequential class switch from IgG3 or IgG1 to downstream isotypes such as IgG4 represents a common effort to limit inflammation in response to a persistent and increasingly abundant antigenic stimulus (84-86). Although such a response may be protective in autoimmune conditions, in the context of cancer, the resultant attenuation of Fab-mediated functions and the IgG4-induced polarization

					Case	s			Control				
	Country	Method of IgM measurement	Types of cancer		Mean age (range), years	Mean serum IgM (SD), mg/dL		Mean age (range), years	Mean serum IgM (SD), mg/dL	Control selection	Matcl	ling	Association
Plesničar, 1972 (35)	Yugoslavia	RID	Uterine	77	54 (30-75, SD 11.8)	94.5 (±31.7) ^{a,b}	38	36 (21-63)	103.0 (土29.6) ^{a,b}	Blood donors	Σ U	1	Negative
Scully, 1982 (36)	UK	RID	Head and neck	26	U/S	137.0 (±62.0)	27	Age-matched	136.0 (±50.0)	U/S	Σ	Σ	Null
Lamoureux, 1982 (37)	Canada	RID	Breast	195	54 (20-84)	177.0 (土139.0)	61	38 (20-47)	210.0 (土65.0)	U/S	Σ	I	Negative
Khanna, 1982 (38)	India	RID	Head and neck	70	U/S (26-70)	112.6 (±27.2)	40	Age-matched	82.5 (±28.5)	U/S	I	Σ	Positive
Rajendran, 1986 (49)	India	RID	Head and neck	32	46 (SD 10.1) ^a	125.8 (土32.4) ^b	25	37 (SD 6.7)	132.5 (土29.2) ^b	U/S	Σ U	I	Negative
Vijayakumar, 1986 (40)	India	RID	Head and neck	196	48 (30-60) ^a	119.9 (土44.1)	100	36 (20-50) ^a	127.2 (±37.4)	Medical	I	I	Negative
			Uterine	172	44 (30-60) ^a	133.8 (土50.5)				campus			Positive
			Breast	166	47 (30-60) ^a	124.6 (±53.7)				volunteers			Null
Vinzenz, 1986 (44)	Austria	Nephelometry	Head and neck	226	U/S	147.9 (土79.9)	49	Age-matched	140.1 (土53.4)	U/S	Σ U	Σ	Positive
Schantz, 1988 (41)	NSA	Immuno-turbidimetry	Head and neck	97	58 (27-82)	130 (土54)	53	59 (43-73)	135.0 (±55.0)	U/S	I	Σ	Negative
Schantz, 1989 (42)	NSA	Immuno-turbidimetry	Head and neck	24	U/S (20-40)	162.0 (土63.0)	32	U/S (20-40)	112 (土47.0)	U/S	I	Σ	Positive
Sadat, 2008 (43)	Bangladesh	Immuno-turbidimetry	Lung	45	52 (20-80,	533.0 (±224.0) ^c	50	45 (20-80,	449.0 (±244.0) ^c	N/S	Σ U	Σ	Positive
					SD 12.0)			SD 13.2)					
			Total	1,326			475						
Abbreviations: AC, affin	ity chromatog.	raphy; AM, age-matched;	GM, gender-match	ed; RID	, radial immunodif	fusion; U/S, Unspeci	ified.						
^b SD calculated from SE ^b	2 101 Eaul sur	upun was required.											
^c Values converted into r	ng/dL.												

Table 3. Case-control studies selected for analysis of the association between serum IgM levels and different types of solid cancers.



Figure 3.

Forest plot for studies comparing mean serum IgM levels in patients with solid cancer and healthy adult controls with associated funnel plot and Egger test for small-study effects.

of macrophages into an immunosuppressive phenotype could be detrimental for tumor immunity (87).

Our meta-analysis also indicated a lack of significant difference in the serum IgM levels of healthy control subjects and patients with newly diagnosed, untreated solid cancer. None of the included studies reported values of serum IgM subtypes. In a recent cohort study of healthy adult Swedish participants, we found an inverse association between serum IgM levels and subsequent risk of developing bladder cancer (88), a finding that is also supported by a recent case-control study of plasma proteome maps (89). Accounting for about 10% of total serum immunoglobulins, IgM is the first immunoglobulin isotype expressed by developing B cells and is responsible for the primary humoral immune response following initial antigen stimulation. Tumor-reactive natural IgM has been shown to be capable of eliminating malignant cells through complement fixation (90), induction of apoptosis (91), and induction of secondary immune responses against neoantigens (92). Epidemiologic evidence suggests that natural IgM antibodies against tumor-associated antigens of epithelial cancers are frequently detected in the serum of both patients with cancer and healthy donors (93) and are often present since birth (94). Interestingly, B-1 B cells from patients with non-small cell lung cancer have been shown to exhibit reduced ability to produce natural IgM (95). Larger prospective studies investigating the association between serum IgM and future solid cancer risk are required to elucidate whether a higher IgM titer can enhance immune surveillance against incipient tumors.

Limitations

Although we excluded studies in which participants were reported to have a comorbid condition, very few studies stated explicitly that patients with solid tumors were specifically assessed for comorbidities or lifestyle factors that could affect serum immunoglobulin levels. In addition, in several studies control subjects were not matched by age or gender, whereas the methods of case (e.g., consecutive) and control selection were rarely reported. This generates uncertainty regarding the validity of our quantitative synthesis of results, as all studies included in the present systematic review were case-control studies. Although we only included studies in which the diagnosis of solid cancer was confirmed by histopathology, several studies did not specify the histologic subtype of the diagnosed malignancy. Furthermore, there was an overrepresentation of studies on head and neck cancer, but very few or no studies investigating other more common malignancies. All of the above factors limit the generalizability of our results. Finally, the persistence of large heterogeneity despite sensitivity analyses by method of immunoglobulin measurement, control matching, and type of solid cancer supports the existence of yet unidentified confounding factors in determining serum immunoglobulin levels in patients with cancer and control subjects, which should be the focus of future systematic investigations of cancer immunity.

The NOS has been widely used in meta-analysis for quality assessment of case-control studies. Although its strengths include the wide adaptability of its criteria and the performance of quality quantification using the star-system, its validity has been a subject of debate (96). In the present meta-analysis, no eligible studies were excluded due to a low NOS score, and all studies were given a score of 6 or above. Furthermore, the use of SMDs based on a random effects model to account for differences in study methodology, as well as subgroup analysis by immunoglobulin measurement and gender-matching, provides additional safeguards against potential differences in the quality of selected studies.

Establishing a causal relationship between cancer immune escape and increased IgA from cross-sectional data is challenging and may differ for each malignancy. It is possible that the skewing of humoral immunity toward a state of relative immunosuppression, which may include immunoglobulin class switching to a raised IgA, may be a late event associated with disease onset or progression and dissemination. An epidemiologic approach to further support this hypothesis would require serial measurements of serum immunoglobulin levels over long periods of follow-up until cancer development and throughout patient care.

Conclusions and Future Perspectives

In summary, the results of the present meta-analysis suggest a possible dysregulation of serum immunoglobulin levels in solid cancer, as reflected by a higher serum IgA in cases compared with control subjects. This finding may reflect a propensity of progression to immune escape as determined by a combination of host factors, environmental factors (microbiota, diet, and drugs affecting the immune system, e.g., NSAIDs and antibiotics), and tumor-specific factors (e.g., tumor mutanome), which can all converge to induce a state of relative immune suppression (29). Chronic antigen exposure might slowly drive T-cell and B-cell exhaustion, as well as attenuation of the antitumor IgG response (e.g., shift from IgG3 or IgG1 to IgG4). Ongoing tumor evolution nurtured by combined T-cell- and immunoglobulin-mediated immunoediting is likely to culminate with skewing toward a Th2-dominant immune response. The dissemination of MDSCs and cancer stem cells in secondary lymphoid organs, as reflected by systemic production of serum IgA, could potentially mark disease dissemination.

Levels of serum immunoglobulin isotypes may be incorporated in future databases and observational studies investigating tumor immunity. Additional analysis of clonality and deep phenotyping of circulating and tumor-infiltrating B cells, as well as characterization of posttranslation modification of immunoglobulins (e.g., glycosylation; refs. 97, 98), could be combined with measurement of other immune parameters, such as cytokine levels. Delineating the timing and association of such changes to genetic, molecular, and clinical disease

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characteristics is likely to be of paramount importance in fully apprehending the dynamics characterizing the relationship of the humoral immune system and cancer development, as well harnessing its potential value as a biomarker.

Disclosure of Potential Conflicts of Interest

S.N. Karagiannis reports receiving a commercial research grant from IGEM Therapeutics Ltd. and has ownership interest (including patents) in antibody technology. No potential conflicts of interest were disclosed by the other authors.

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