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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 meta-analysis, 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 difference (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.

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).

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 TGFβ) 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 tumor-infiltrating B cells has been associated with improved outcomes in an increasing number of solid cancers (13). B cells can act as antigen-presenting 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 TGFβ 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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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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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 case–control 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. Vijayakumar 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 meta-analysis 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

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

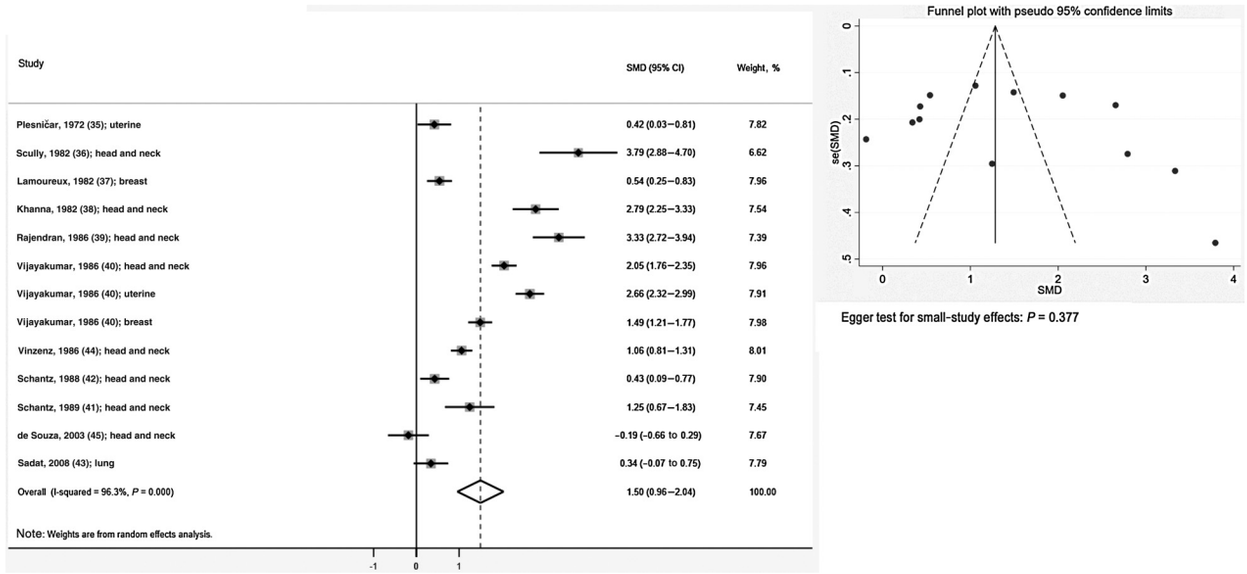

Figure 1.
Forest plot for studies comparing mean serum IgA levels in patients with solid cancer and healthy adult controls with associated funnel plot and Egger test for small-study effects.

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 meta-analysis 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 methodology, 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, TGFβ, 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

Table 1. Case–control studies selected for analysis of the association between serum IgA levels and different types of solid cancers.

				Cases			Control					
Study	**Country**	**Method of IgA measurement**	**Types of cancer**	***n***	**Mean age (range), years**	**Mean serum IgA (SD), mg/dL**	***n***	**Mean age (range), years**	**Mean serum IgA (SD), mg/dL**	**Control selection**	**Matching**	**Association**
Plesničar, 1972 (35)	Yugoslavia	RID	Uterine	77	54 (30–75, SD 11.8)	195.1 (±43.3)[a,b]	38	36 (21–63)	175.0 (±56.1)[a,b]	Blood donors	GM —	Positive
Scully, 1982 (36)	UK	RID	Head and neck	26	U/S	379.0 (±38.0)	27	Age-matched	256.0 (±26.0)	U/S	GM AM	Positive
Lamoureux, 1982 (37)	Canada	RID	Breast	196	54 (20–84)	274.0 (±168.0)	61	38 (20–47)	192.0 (±78.0)	U/S	GM —	Positive
Khanna, 1982 (38)	India	RID	Head and neck	70	U/S (26–70)	358.7 (±79.2)	40	Age-matched	168.3 (±42.5)	U/S	— AM	Positive
Rajendran, 1986 (39)	India	RID	Head and neck	50	46 (SD 10.1)[a]	327.5 (±41.4)[b]	50	37 (SD 6.7)	211.50 (±26.7)[b]	U/S	GM —	Positive
Vijayakumar, 1986 (40)	India	RID	Head and neck	196	48 (30–60)[a]	307.8 (±56.4)	100	36[a] (20–50)	206.50 (±31.2)	Medical campus volunteers	— —	Positive
			Uterine	172	44 (30–60)[a]	339.4 (±58.3)						Positive
			Breast	166	47 (30–60)[a]	284.3 (±61.2)						Positive
Vinzenz, 1986 (44)	Austria	Nephelometry	Head and neck	216	U/S	346.4 (±166.3)	100	Age-matched	192.7 (±82.0)	U/S	GM AM	Positive
Schantz, 1988 (41)	USA	Immuno-turbidimetry	Head and neck	97	58 (27–82)	263.0 (±134.0)	53	59 (43–73)	212.0 (±85)	U/S	— AM	Positive
Schantz, 1989 (42)	USA	Immuno-turbidimetry	Head and neck	24	U/S (20–40)	275.0 (±114.0)	32	U/S (20–40)	161.0 (±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 (±194.1)	U/S	GM AM	Negative
Sadat, 2008 (43)	Bangladesh	Immuno-turbidimetry	Lung	45	52.3 (25–80, SD 12.0)	506 (±188)[c]	50	52.9 (25–80, SD 13.2)	450 (±140)[c]	U/S	GM AM	Positive
			Total	1,351			560					

Abbreviations: AM, age-matched; GM, gender-matched; RID, radial immunodiffusion; U/S, Unspecified.
[a]Amalgamation of values for each subgroup was required.
[b]SD calculated from SEM.
[c]Values converted into mg/dL.

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

				Cases			Control					
	Country	Method of IgG measurement	Types of cancer	*n*	Mean age (range), years	Mean serum IgG (SD), mg/dL	*n*	Mean age (range), years	Mean serum IgG (SD), mg/dL	Control selection	Matching	Association
Plesničar, 1972 (35)	Yugoslavia	RID	Uterine	77	54 (30–75, SD 11.8)	1,253.8 (±247.0)[a,b]	38	36 (21–63)	1,035.0 (±163.4)[a,b]	Blood donors	GM —	Positive
Scully, 1982 (36)	UK	RID	Head and neck	26	U/S	1,449.0 (±559.0)	27	Age-matched	1,479.0 (±106.0)	U/S	GM AM	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	GM —	Negative
Khanna, 1982 (38)	India	RID	Head and neck	70	U/S (26–70)	1,280.3 (±227.4)	40	Age-matched	1,361.0 (±233.7)	U/S	— AM	Negative
Rajendran, 1986 (39)	India	RID	Head and neck	32	46 (SD 10.1)[a]	1,429.7 (±461.7)[b]	25	37 (SD 6.7)	1,495.4 (±422.7)[b]	U/S	GM —	Negative
Vijayakumar, 1986 (40)	India	RID	Head and neck	196	48 (30–60)[a]	1,489.7 (±411.3)	100	36 (20–50)[a]	1,521.4 (±372.7)	Medical campus volunteers	— —	Negative
			Uterine	172	44 (30–60)[a]	1,687.8 (±381.6)						Positive
			Breast	166	47 (30–60)[a]	1,465.6 (±421.4)						Negative
Vinzenz, 1986 (44)	Austria	Nephelometry	Head and neck	223	U/S	1,194.3 (±372.9)	51	Age-matched	1,091.6 (±252.2)	U/S	GM AM	Positive
Schantz, 1988 (41)	USA	Immuno-turbidimetry	Head and neck	97	58 (27–82)	1,010.0 (±293.0)	53	59 (43–73)	951.0 (±217.0)	U/S	— AM	Positive
Schantz, 1989 (42)	USA	Immuno-turbidimetry	Head and neck	24	U/S (20–40)	1,142.0 (±254.0)	32	U/S (20–40)	904.0 (±231.0)	U/S	— AM	Positive
Schauenstein, 1996 (46)	Austria	AC	Ovary and cervix	207	U/S (21–85)	960.0 (±431.6)[b,c]	135	Age-matched	1,090.0 (±232.3)[b,c]	U/S	GM AM	Negative
Schauenstein, 1997 (47)	Austria	AC	Colorectal	36	69 (U/S)	990.0 (±300.0)[b,c]	162	Age-matched	1,030.0 (±254.6)[b,c]	U/S	— AM	Negative
Anderhuber, 1999 (48)	Austria	AC	Head and neck	74	U/S	960.0 (±344.1)[b,c]	174	Age-matched	1,030 (±263.8)[b,c]	U/S	GM AM	Negative
Sadat, 2008 (43)	Bangladesh	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 (±802)[c]	U/S	GM AM	Negative
Saito, 2017 (49)	Japan	ELISA	Gastric	100	U/S	9,05.1 (±412.2)	27	67 (SD 10.3)	1,037.0 (±293.3)	U/S	— AM	Negative
			Total	1,745			1,032					

Abbreviations: AC, affinity chromatography; AM, age-matched; GM, gender-matched; RID, radial immunodiffusion; U/S, Unspecified.
[a]Amalgamation of values for each subgroup was required.
[b]SD calculated from SEM.
[c]Values converted into mg/dL.

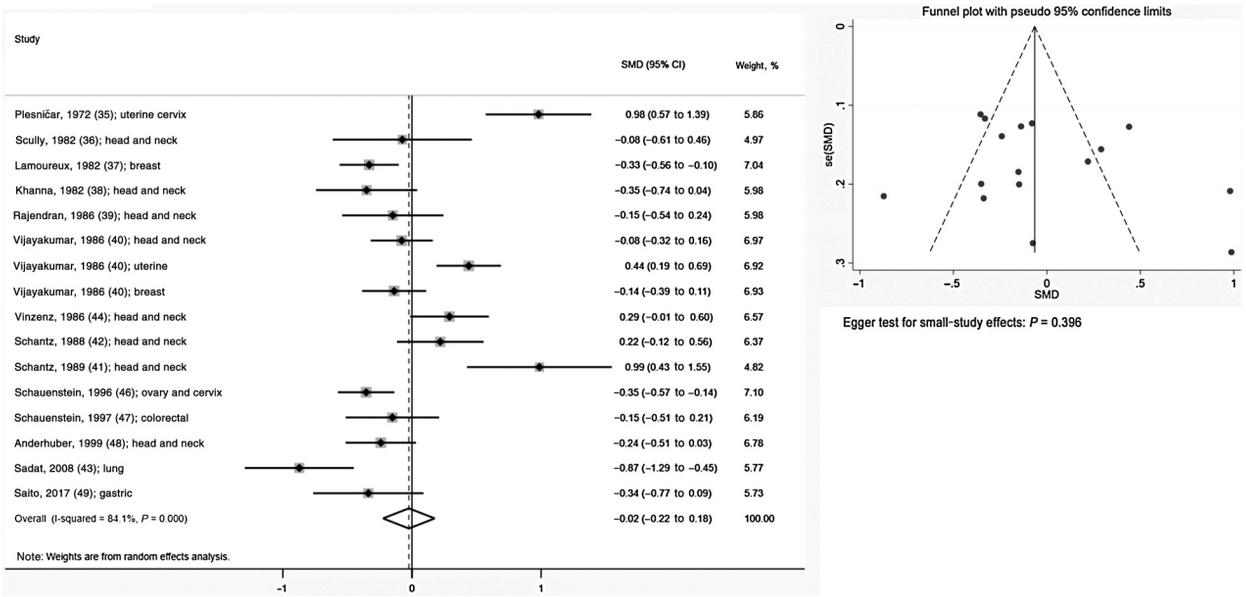

Figure 2.
Forest plot for studies comparing mean serum IgG levels in patients with solid cancer and healthy adult controls with associated funnel plot and Egger test for small-study effects.

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, TGFβ, 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 FcαRI 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 TGFβ. 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 meta-analysis 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

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

				Cases			Control					
	Country	Method of IgM measurement	Types of cancer	*n*	Mean age (range), years	Mean serum IgM (SD), mg/dL	*n*	Mean age (range), years	Mean serum IgM (SD), mg/dL	Control selection	Matching	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 (±29.6)[a,b]	Blood donors	GM —	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	GM AM	Null
Lamoureux, 1982 (37)	Canada	RID	Breast	195	54 (20–84)	177.0 (±139.0)	61	38 (20–47)	210.0 (±65.0)	U/S	GM —	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	— AM	Positive
Rajendran, 1986 (49)	India	RID	Head and neck	32	46 (SD 10.1)[a]	125.8 (±32.4)[b]	25	37 (SD 6.7)	132.5 (±29.2)[b]	U/S	GM —	Negative
Vijayakumar, 1986 (40)	India	RID	Head and neck	196	48 (30–60)[a]	119.9 (±44.1)	100	36 (20–50)[a]	127.2 (±37.4)	Medical campus volunteers	— —	Negative
			Uterine	172	44 (30–60)[a]	133.8 (±50.5)						Positive
			Breast	166	47 (30–60)[a]	124.6 (±53.7)						Null
Vinzenz, 1986 (44)	Austria	Nephelometry	Head and neck	226	U/S	147.9 (±79.9)	49	Age-matched	140.1 (±53.4)	U/S	GM AM	Positive
Schantz, 1988 (41)	USA	Immuno-turbidimetry	Head and neck	97	58 (27–82)	130 (±54)	53	59 (43–73)	135.0 (±55.0)	U/S	— AM	Negative
Schantz, 1989 (42)	USA	Immuno-turbidimetry	Head and neck	24	U/S (20–40)	162.0 (±63.0)	32	U/S (20–40)	112 (±47.0)	U/S	— AM	Positive
Sadat, 2008 (43)	Bangladesh	Immuno-turbidimetry	Lung	45	52 (20–80, SD 12.0)	533.0 (±224.0)[c]	50	45 (20–80, SD 13.2)	449.0 (±244.0)[c]	U/S	GM AM	Positive
			Total	1,326			475					

Abbreviations: AC, affinity chromatography; AM, age-matched; GM, gender-matched; RID, radial immunodiffusion; U/S, Unspecified.
[a]Amalgamation of values for each subgroup was required.
[b]SD calculated from SEM.
[c]Values converted into mg/dL.

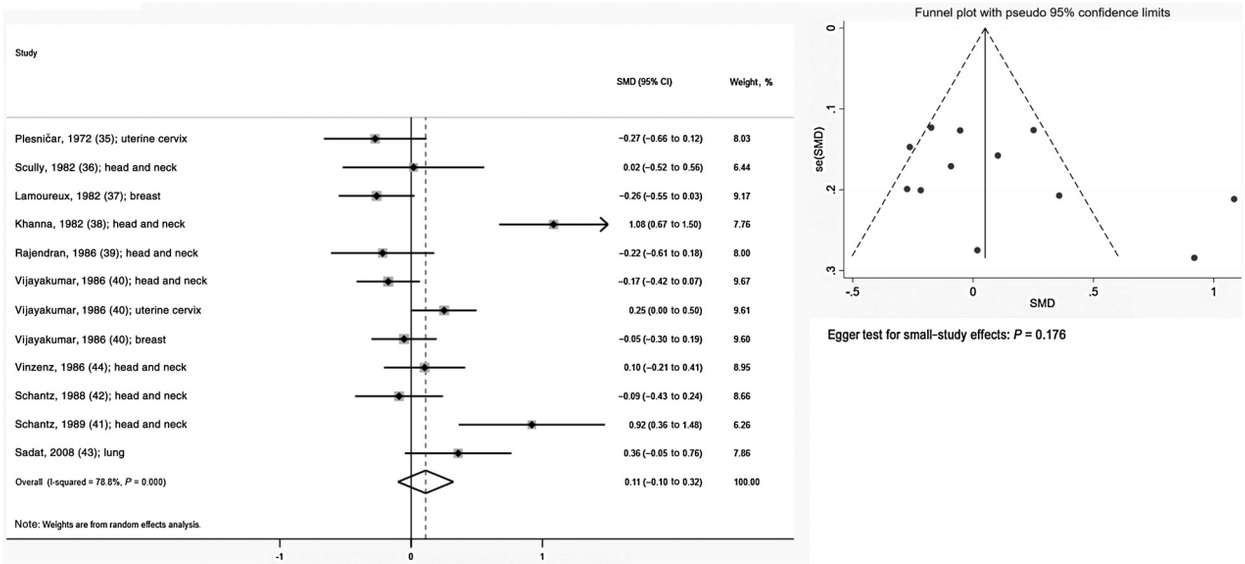

Figure 3.
Forest plot for studies comparing mean serum IgM levels in patients with solid cancer and healthy adult controls with associated funnel plot and Egger test for small-study effects.

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 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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References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646–74.
2. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329–60.
3. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350–5.
4. Yuen GJ, Demissie E, Pillai S. B lymphocytes and cancer: a love-hate relationship. Trends Cancer 2016;2:747–57.
5. de Visser KE, Korets LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell 2005;7: 411–23.
6. Shah S, Divekar AA, Hilchey SP, Cho HM, Newman CL, Shin SU, et al. Increased rejection of primary tumors in mice lacking B cells: inhibition of anti-tumor CTL and TH1 cytokine responses by B cells. Int J Cancer 2005;117:574–86.
7. Sarvaria A, Madrigal JA, Saudemont A. B cell regulation in cancer and anti-tumor immunity. Cell Mol Immunol 2017;14:662–74.
8. Bodogai M, Moritoh K, Lee-Chang C, Hollander CM, Sherman-Baust CA, Wersto RP, et al. Immunosuppressive and prometastatic functions of myeloid-derived suppressive cells rely upon education from tumor-associated B cells. Cancer Res 2015;75:3456–65.
9. Khan AR, Hams E, Floudas A, Sparwasser T, Weaver CT, Fallon PG. PD-L1hi B cells are critical regulators of humoral immunity. Nat Commun 2015;6:5997.
10. Andreu P, Johansson M, Affara NI, Pucci F, Tan T, Junankar S, et al. FcRgamma activation regulates inflammation-associated squamous carcinogenesis. Cancer Cell 2010;17:121–34.
11. Karagiannis P, Villanova F, Josephs DH, Correa I, Van Hemelrijck M, Hobbs C, et al. Elevated IgG4 in patient circulation is associated with the risk of disease progression in melanoma. Oncoimmunology 2015;4:e1032492.
12. Gu Y, Liu Y, Fu L, Zhai L, Zhu J, Han Y, et al. Tumor-educated B cells selectively promote breast cancer lymph node metastasis by HSPA4-targeting IgG. Nat Med 2019;25:312–22.
13. Wouters MCA, Nelson BH. Prognostic significance of tumor-infiltrating B cells and plasma cells in human cancer. Clin Cancer Res 2018;24:6125–35.
14. Germain C, Gnjatic S, Dieu-Nosjean MC. Tertiary lymphoid structure-associated B cells are key players in anti-tumor immunity. Front Immunol 2015;6:67.
15. Bruno TC, Ebner PJ, Moore BL, Squalls OG, Waugh KA, Eruslanov EB, et al. Antigen-presenting intratumoral B cells affect CD4(+) TIL phenotypes in non-small cell lung cancer patients. Cancer Immunol Res 2017;5:898–907.
16. Teillaud JL, Dieu-Nosjean MC. Tertiary lymphoid structures: an anti-tumor school for adaptive immune cells and an antibody factory to fight cancer? Front Immunol 2017;8:830.
17. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med 2015;21:938–45.
18. Wang SS, Liu W, Ly D, Xu H, Qu L, Zhang L. Tumor-infiltrating B cells: their role and application in anti-tumor immunity in lung cancer. Cell Mol Immunol 2019; 16:6–18.
19. Kroeger DR, Milne K, Nelson BH. Tumor-infiltrating plasma cells are associated with tertiary lymphoid structures, cytolytic T-cell responses, and superior prognosis in ovarian cancer. Clin Cancer Res 2016;22:3005–15.
20. Schmidt M, Hellwig B, Hammad S, Othman A, Lohr M, Chen Z, et al. A comprehensive analysis of human gene expression profiles identifies stromal immunoglobulin kappa C as a compatible prognostic marker in human solid tumors. Clin Cancer Res 2012;18:2695–703.
21. Berntsson J, Nodin B, Eberhard J, Micke P, Jirstrom K. Prognostic impact of tumour-infiltrating B cells and plasma cells in colorectal cancer. Int J Cancer 2016;139:1129–39.
22. Shalapour S, Font-Burgada J, Di Caro G, Zhong Z, Sanchez-Lopez E, Dhar D, et al. Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. Nature 2015;521:94–8.
23. Liu Q, Niu Z, Li Y, Wang M, Pan B, Lu Z, et al. Immunoglobulin G4 (IgG4)-positive plasma cell infiltration is associated with the clinicopathologic traits and prognosis of pancreatic cancer after curative resection. Cancer Immunol Immunother 2016;65:931–40.
24. Bosisio FM, Wilmott JS, Volders N, Mercier M, Wouters J, Stas M, et al. Plasma cells in primary melanoma. Prognostic significance and possible role of IgA. Mod Pathol 2016;29:347–58.
25. Chiaruttini G, Mele S, Opzoomer J, Crescioli S, Ilieva KM, Lacy KE, et al. B cells and the humoral response in melanoma: the overlooked players of the tumor microenvironment. Oncoimmunology 2017;6:e1294296.

26. Shalapour S, Lin XJ, Bastian IN, Brain J, Burt AD, Aksenov AA, et al. Inflammation-induced IgA+ cells dismantle anti-liver cancer immunity. Nature 2017; 551:340–5.
27. Egbuniwe IU, Karagiannis SN, Nestle FO, Lacy KE. Revisiting the role of B cells in skin immune surveillance. Trends Immunol 2015;36:102–11.
28. Van Hemelrijck M, Garmo H, Binda E, Hayday A, Karagiannis SN, Hammar N, et al. Immunoglobulin E and cancer: a meta-analysis and a large Swedish cohort study. Cancer Causes Control 2010;21:1657–67.
29. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature 2017;541:321–30.
30. Moher D, Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
31. Ritchie R, Palomaki G, Neveux L, Navolotskaia O, Ledue T, Craig W. Reference distributions for immunoglobulins A, G, and M: a practical, simple, and clinically relevant approach in a large cohort. J Clin Lab Anal 1998;12:363–70.
32. Lock RJ, Unsworth DJ. Immunoglobulins and immunoglobulin subclasses in the elderly. Ann Clin Biochem 2003;40(Pt 2):143–8.
33. Wells G, Shea B, O'Connell J, Robertson J, Peterson V, Welch V, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis [accessed 2018 Nov 10]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
34. Deeks J, Altman D, Bradburn M. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith G, Altman D, editors. Padstow: International Ltd; 2001.
35. Plesničar S. Immunoglobulins in carcinoma of the uterine cervix. Acta Radiol Ther Phys Biol 1972;11:37–47.
36. Scully C. Immunological abnormalities in oral carcinoma and oral keratosis. J Max Fac Surg 1982;10:113–5.
37. Lamoureux G, Mandeville R, Poisson R, Legault-Poisson S, Jolicoeur R. Biologic markers and breast cancer: a multiparametric study- 1. Increased serum protein levels. Cancer 1982;49:502–12.
38. Khanna NN, Das SN, Khanna S. Serum immunoglobulins in squamous cell carcinoma of the oral cavity. J Surg Oncol 1982;20:46–8.
39. Rajendran R, Sugathan CK, Remani P, Ankathil R, Vijayakumar T. Cell mediated and humoral immune responses in oral submucous fibrosis. Cancer 1986;58: 2628–31.
40. Vijayakumar T, Ankathil R, Remani P, Sasidharan VK, Vijayan KK, Vasudevan DM. Serum immunoglobulins in patients with carcinoma of the oral cavity, uterine cervix and breast. Cancer Immunol Immunother 1986;22:76–9.
41. Schantz SP, Liu FJ. An immunologic profile of young adults with head and neck cancer. Cancer 1989;64:1232–7.
42. Schantz SP, Liu FJ, Taylor D, Beddingfield N, Weber RS. The relationship of circulating IgA to cellular immunity in head and neck cancer patients. Laryngoscope 1988;86(6 Pt 1):671–8.
43. Sadat AFMN, Hossain I, Hossain K, Reza S, Nahar Z, Islam SKN, et al. Serum trace elements and immunoglobulin profile in lung cancer patients. J Appl Res 2008;8:24–33.
44. Vinzenz K, Pavelka R, Schönthal E, Zekert F. Serum immunoglobulin levels in patients with head and neck cancer (IgE, IgA, IgM, IgG). Oncology 1986;43: 316–22.
45. de Souza RM, Lehn CN, Denardin OV. Serum and salivary immunoglobulin A levels in patients with cancer of the mouth and oropharynx. [article in Portuguese] Rev Assoc Med Bras (1992) 2003;49:40–4.
46. Schauenstein E, Lahousen M, Weblacher M, Steinschifter W, Estelberger W, Schauenstein K. Selective decrease in serum immunoglobulin G1. A tissue nonspecific tumor marker detecting early stages of gynecologic malignant disease with high efficiency. Cancer 1996;78:511–6.
47. Schauenstein E, Rabl H, Steinschifter W, Hirschmann C, Estelberger W, Schauenstein K. Selective decrease of serum immunoglobulin G1 as a marker of malignant transformation in colorectal tissue. Cancer 1997;79: 1482–6.
48. Anderhuber W, Steinschifter W, Schauenstein E, Gotschuli A, Habermann W, Fischer M, et al. The IgG1/G2 subclass shift–a sensitive, tissue non-specific marker for malignancy. Diagnostic performance with squamous cell carcinoma of the head and neck. Br J Cancer 1999;79:1777–81.
49. Saito H, Miyatani K, Kono Y, Murakami Y, Kuroda H, Matsunaga T, et al. Decreased serum concentration of total IgG is related to tumor progression in gastric cancer patients. Yonago Acta Med 2017;60:119–25.
50. Clayman GL, Savage HE, Ainslie N, Liu FJ, Schantz SP. Serologic determinants of survival in patients with squamous cell carcinoma of the head and neck. Am J Surg 1990;160:434–8.
51. Torisu T, Takata Y, Ansai T, Soh I, Awano S, Sonoki K, et al. IgA level is associated with risk for mortality in an eighty-year-old population. Gerontology 2009;55:179–85.
52. Gonzalez-Quintela A, Alende R, Gude F, Campos J, Rey J, Meijide LM, et al. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. Clin Exp Immunol 2008;151:42–50.
53. Howell WM, Rose-Zerilli MJ. Cytokine gene polymorphisms, cancer susceptibility, and prognosis. J Nutr 2007;137 Suppl 1:194S–9S.
54. Vandenbroeck K. Cytokine gene polymorphisms and human autoimmune disease in the era of genome-wide association studies. J Interferon Cytokine Res 2012;32:139–51.
55. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer 2008;8:887–99.
56. Wang P, An J, Zhu Y, Wan X, Zhang H, Xi S, et al. Association of three promoter polymorphisms in interleukin-10 gene with cancer susceptibility in the Chinese population: a meta-analysis. Oncotarget 2017;8:62382–99.
57. Shi Q, Wang X, Cai C, Yang S, Huo N, Liu H. Association between TGF-beta1 polymorphisms and head and neck cancer risk: a meta-analysis. Front Genet 2017;8:169.
58. Goedert JJ, Hua X, Bielecka A, Okayasu I, Milne GL, Jones GS, et al. Postmenopausal breast cancer and oestrogen associations with the IgA-coated and IgA-noncoated faecal microbiota. Br J Cancer 2018;118:471–9.
59. Urbaniak C, Gloor GB, Brackstone M, Scott L, Tangney M, Reid G. The microbiota of breast tissue and its association with breast cancer. Appl Environ Microbiol 2016;82:5039–48.
60. Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science 2018;359: 1366–70.
61. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359:91–7.
62. Schroeder HW Jr, Cavacini L. Structure and function of immunoglobulins. J Allergy Clin Immunol 2010;125 Suppl 2:S41–52.
63. Nakajima A, Vogelzang A, Maruya M, Miyajima M, Murata M, Son A, et al. IgA regulates the composition and metabolic function of gut microbiota by promoting symbiosis between bacteria. J Exp Med 2018;215:2019–34.
64. Kawamoto S, Maruya M, Kato LM, Suda W, Atarashi K, Doi Y, et al. Foxp3(+) T cells regulate immunoglobulin a selection and facilitate diversification of bacterial species responsible for immune homeostasis. Immunity 2014;41:152–65.
65. Ruane D, Chorny A, Lee H, Faith J, Pandey G, Shan M, et al. Microbiota regulate the ability of lung dendritic cells to induce IgA class-switch recombination and generate protective gastrointestinal immune responses. J Exp Med 2016;213: 53–73.
66. Audiger C, Rahman MJ, Yun TJ, Tarbell KV, Lesage S. The importance of dendritic cells in maintaining immune tolerance. J Immunol 2017;198:2223–31.
67. Pao W, Ooi CH, Birzele F, Ruefli-Brasse A, Cannarile MA, Reis B, et al. Tissue-specific immunoregulation: a call for better understanding of the "Immunostat" in the context of cancer. Cancer Discov 2018;8:395–402.
68. Domogalla MP, Rostan PV, Raker VK, Steinbrink K. Tolerance through education: how tolerogenic dendritic cells shape immunity. Front Immunol 2017;8: 1764.
69. Veglia F, Gabrilovich DI. Dendritic cells in cancer: the role revisited. Curr Opin Immunol 2017;45:43–51.
70. Hughes NR. Serum concentrations of γG, γA, and γM immunoglobulins in patients with carcinoma, melanoma, and sarcoma. J Natl Cancer Inst 1971;46: 1015–28.
71. Borsutzky S, Cazac BB, Roes J, Guzmán CA. TGF-β receptor signaling is critical for mucosal IgA responses. J Immunol 2004;173:3305–9.
72. Dedobbeleer O, Stockis J, van der Woning B, Coulie PG, Lucas S. Cutting edge: active TGF-beta1 released from GARP/TGF-beta1 complexes on the surface of stimulated human B lymphocytes increases class-switch recombination and production of IgA. J Immunol 2017;199:391–6.
73. Konkel JE, Chen W. Balancing acts: the role of TGF-beta in the mucosal immune system. Trends Mol Med 2011;17:668–76.
74. Mkaddem SB, Christou I, Rossato E, Berthelot L, Lehuen A, Monteiro RC. IgA, IgA receptors, and their anti-inflammatory properties. Curr Top Microbiol Immunol 2014;382:221–35.

75. Ben Mkaddem S, Rossato E, Heming N, Monteiro RC. Anti-inflammatory role of the IgA Fc receptor (CD89): from autoimmunity to therapeutic perspectives. Autoimmun Rev 2013;12:666–9.
76. Pilette C, Detry B, Guisset A, Gabriels J, Sibille Y. Induction of interleukin-10 expression through Fcalpha receptor in human monocytes and monocyte-derived dendritic cells: role of p38 MAPKinase. Immunol Cell Biol 2010;88:486–93.
77. Saha C, Das M, Patil V, Stephen-Victor E, Sharma M, Wymann S, et al. Monomeric immunoglobulin A from plasma inhibits human Th17 responses in vitro independent of FcαRI and DC-SIGN. Front Immunol 2017;8:275.
78. Lang S, Bruderek K, Kaspar C, Hoing B, Kanaan O, Dominas N, et al. Clinical relevance and suppressive capacity of human myeloid-derived suppressor cell subsets. Clin Cancer Res 2018;24:4834–44.
79. Xu X, Meng Q, Erben U, Wang P, Glauben R, Kuhl AA, et al. Myeloid-derived suppressor cells promote B-cell production of IgA in a TNFR2-dependent manner. Cell Mol Immunol 2017;14:597–606.
80. Kronberger L, Steinschifter W, Weblacher M, Estelberger W, Liebmann PM, Rabl H, et al. Selective decrease of serum immunoglobulin G1 as marker for early stages of invasive breast cancer. Breast Cancer Res Treat 2000;64:193–9.
81. Zhang H, Li P, Wu D, Xu D, Hou Y, Wang Q, et al. Serum IgG subclasses in autoimmune diseases. Medicine (Baltimore) 2015;94:e387.
82. Wu J, Ma XL, Tian L, Zhang CY, Wang BL, Hu YY, et al. Serum IgG4:IgG ratio predicts recurrence of patients with hepatocellular carcinoma after curative resection. J Cancer 2017;8:1338–46.
83. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460–71.
84. Kitaura K, Yamashita H, Ayabe H, Shini T, Matsutani T, Suzuki R. Different somatic hypermutation levels among antibody subclasses disclosed by a new next-generation sequencing-based antibody repertoire analysis. Front Immunol 2017;8:389.
85. Jspeert HI, van Schouwenburg PA, van Zessen D, Pico-Knijnenburg I, Driessen GJ, Stubbs AP, et al. Evaluation of the antigen-experienced B-cell receptor repertoire in healthy children and adults. Front Immunol 2016;7:410.
86. Saul L, Ilieva KM, Bax HJ, Karagiannis P, Correa I, Rodriguez-Hernandez I, et al. IgG subclass switching and clonal expansion in cutaneous melanoma and normal skin. Sci Rep 2016;6:29736.
87. Jensen-Jarolim E, Turner MC, Karagiannis SN. AllergoOncology: IgE- and IgG4-mediated immune mechanisms linking allergy with cancer and their translational implications. J Allergy Clin Immunol 2017;140:982–4.
88. Peppas I, Sollie S, Josephs DH, Hammar N, Walldius G, Karagiannis SN, et al. Serum immunoglobulin levels and the risk of bladder cancer in the AMORIS Cohort. Cancer Epidemiol 2019;62:101584.
89. Lemanska-Perek A, Lis-Kuberka J, Lepczynski A, Dratwa-Chalupnik A, Tupikowski K, Katnik-Prastowska I, et al. Potential plasma biomarkers of bladder cancer identified by proteomic analysis: a pilot study. Adv Clin Exp Med 2019;28:339–46.
90. Díaz-Zaragoza M, Hernández-Ávila R, Viedma-Rodríguez R, Arenas-Aranda D, Ostoa-Saloma P. Natural and adaptive IgM antibodies in the recognition of tumor-associated antigens of breast cancer (review). Oncol Rep 2015;34:1106–14.
91. Kaveri SV, Silverman GJ, Bayry J. Natural IgM in immune equilibrium and harnessing their therapeutic potential. J Immunol 2012;188:939–45.
92. Atif SM, Gibbings SL, Redente EF, Camp FA, Torres RM, Kedl RM, et al. Immune surveillance by natural IgM is required for early neoantigen recognition and initiation of adaptive immunity. Am J Respir Cell Mol Biol 2018;59:580–91.
93. Brändlein S, Pohle T, Ruoff N, Wozniak E, Müller-Hermelink HK, Vollmers HP. Natural IgM antibodies and immunosurveillance mechanisms against epithelial cancer cells in humans. Cancer Res 2003;63:7995–8005.
94. Madi A, Bransburg-Zabary S, Maayan-Metzger A, Dar G, Ben-Jacob E, Cohen IR. Tumor-associated and disease-associated autoantibody repertoires in healthy colostrum and maternal and newborn cord sera. J Immunol 2015;194:5272–81.
95. Hernandez AM, Rodriguez-Zhurbenko N, Quach TD, Hopkins TJ, Rothstein TL. The advancing age affects the frequency, functions and antibody repertoire of human B-1 cells, which secrete anti-tumor antibodies. J Immunol 2017;198:130.14.
96. Stang A, Jonas S, Poole C. Case study in major quotation errors: a critical commentary on the Newcastle-Ottawa scale. Eur J Epidemiol 2018;33:1025–31.
97. Reuschenbach M, von Knebel Doeberitz M, Wentzensen N. A systematic review of humoral immune responses against tumor antigens. Cancer Immunol Immunother 2009;58:1535–44.
98. Wahl A, van den Akker E, Klaric L, Stambuk J, Benedetti E, Plomp R, et al. Genome-wide association study on immunoglobulin G glycosylation patterns. Front Immunol 2018;9:277.