Antibodies as biomarkers for cancer risk: a systematic review

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Summary
Increasing evidence has linked the humoral immune response with the development of various cancers. Therefore, there is growing interest in investigating the predictive value of antibodies to assess overall and tissue site-specific cancer risk. Given the large amount of antibody types and the broad scope of the search (i.e. cancer risk), the primary aim of this systematic review was to present an overview of the most researched antibodies (i.e. immunoglobulin (Ig) isotypes (IgG, IgM, IgA, and IgE), tumour and self-antigen-reactive antibodies, infection-related antibodies) in relation to overall and site-specific cancer risk. We identified various antibody types that have been associated with the risk of cancer. While no significant associations were found for IgM serum levels, studies found an inconsistent association among IgE, IgA, and IgG serum levels in relation to cancer risk. When evaluating antibodies against infectious agents, most studies reported a positive link with specific cancers known to be associated with the specific agent recognized by serum antibodies (i.e. helicobacter pylori and gastric cancer, hepatitis B virus and hepatocellular carcinoma, and human papillomavirus and cervical cancer). Several reports identified autoantibodies, as single biomarkers (e.g. anti-p53, anti-MUC1, and anti-CA125) but especially in panels of multiple autoantibodies, to have potential as diagnostic biomarkers for specific cancer types. Overall, there is emerging evidence associating certain antibodies to cancer risk, especially immunoglobulin isotypes, tumour-associated antigen-specific, and self-reactive antibodies. Further experimental studies are necessary to assess the efficacy of specific antibodies as markers for the early diagnosis of cancer.

Keywords: antibodies, biomarkers, cancer, early detection, tumor-associated antigens, immunoglobulin

Abbreviations: ADCC: antibody-dependent cell cytotoxicity; ADCP: antibody-dependent cell phagocytosis; ANCA: antineutrophil cytoplasmic antibody; Anti-EA: early antigen; Anti-HBc: hepatitis core antigen; Anti-HBs: hepatitis B specific antigen; Anti-UPF1: uperlinki II antibody; Anti-VCA: viral capsid antigen; ASK1: additional sex combs like 2; BARD1: BRCA1-associated RING domain protein 1; BKV: BK virus; BIRC: baculoviral inhibitors of apoptosis repeat containing; BRCA: breast cancer gene; CaggA: cytotoxic associated gene A; CAGE: cancer/testis antigen gene; CA125: cancer antigen 125; CDC: complement-depending cytotoxicity; CMV: cytomegalovirus; CRC: colorectal cancer; C1q: complement component 1q; EBNA: Epstein-Barr nuclear antigen; EBV: Epstein-Barr virus; EPIC: European Prospective Investigation into Cancer and Nutrition; FcRs: FC receptors; FNA: fine needle aspiration biopsy; FOXP3: forkhead box P3; GAGE7: G Antigen 7; GBV: Great Britain virus; GC: gastric cancer; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HE4: human epididymis protein 4; HER2: human epidermal growth factor receptor 2; HPV: human papillomavirus; Ig: immunoglobulin; IgA: immunoglobulin A; IgE: immunoglobulin E; IFNBP: insulin-like growth factor-binding protein; IgG: immunoglobulin G; IgG4-RD: immunoglobulin G4 related disease; IgM: immunoglobulin M; JCV: John Cunningham virus; LaSSB: Sjögren’s-syndrome-related antigen B; MAGEA1: melanoma-associated antigen 1; MCV: molluscum contagiosum virus; MDMD2: mouse double minute 2 homolog; MEG3: maternally expressed gene 3; mTSA: mutated tumour specific antigen; MUC1: mucin 1; Neu5Gc: N-glycolylneuraminic acid; nmTAA: non-mutational tumour-associated antigen; NPC: nasopharyngeal carcinoma; NPM1: nucleophosmin; NXP2: nuclear matrix protein; NY-ESO-1: New York esophageal squamous cell carcinoma-1; PDIAB: protein disulphide isomerase family A: member 6; PGP9.5: protein gene product 9.5; PLAT: tissue plasminogen activator; PRDX: peroxiredoxins; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PSA: prostate-specific antigen; RalA: Ras-related protein Ral-A; RD: related disease; RNASP: ribonucleic acid polymerase; RNP-3: U11/U12 small nuclear ribonucleoprotein; Ro/SSA: Sjögren’s-syndrome-related antigen A; RPA: replication protein A; SAE: small ubiquitin-like modifier activating enzyme; SBP1: selenium-binding protein 1; SCA: squamous cell carcinoma antigen; SDCCAG3: serologically defined colon cancer antigen-3; SR: self-reported; SRP: anti-signal recognition particle; TAA: tumour-associated antigen; Tg: anti-thyroglobulin; TIF1: transcriptional intermediary factor; TOPO: topoisomerase; TPO: anti-thyroid peroxidase; TTG: tissue transglutaminase; VacA: vacuolating cytotoxin.
Introduction

Immunoglobulins (Ig) are tetrameric glycoproteins produced by B cells as part of the humoral immune response. Their structure is composed of a Fab region, consisting of two identical Fab fragments, including the light chain and part of the heavy chain; a fragment crystallizable (Fc) region formed by the constant portion of the two heavy chains; and a hinge region, joining the Fab and Fc regions (Fig. 1). The heavy chain defines the isotype of the antibody, and the Fc portion can bind cognate Fc receptors (FcRs) on immune cells and members of the complement cascade including complement component 1q (C1q) and is responsible for antibody-mediated effector functions such as antibody-dependent cell cytotoxicity (ADCC), antibody-dependent cell phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) [1]. Antibodies, binding to FcRs expressed on immune cells, can also influence immune cell phenotype, and polarization and once complexed with antigens to form immune complexes, they can be internalized to facilitate antigen presentation. Human B cells can express five antibody classes (divided into nine antibody isotypes, IgD, IgM, IgG [1–4], IgA [1, 2], and IgE). Each class recognizes specific cognate FcRs or C1q with different affinity and thus differ in their abilities to trigger effector functions such as ADCC, ADCP, and CDC. Therefore, antibody isotype may significantly influence the immune response that may protect not only against external pathogens but also from the rise of cancer. The IgM isotype is involved in primary immune response and in its secreted form it can assemble in high avidity pentamers. IgG is the predominant class of antibodies in the human serum. IgG subclasses like IgG1 and IgG3 have a high affinity for activating FcγRs and C1q resulting in a high capacity to trigger ADC and activate the complement cascade. IgG2 and IgG4 subclasses have instead poor capacity to fix complement and lower ability to bind activating FcγRs compared to IgG1, and IgG4 has a relatively high affinity for the inhibitory receptor FcγRIIB resulting in negative immune effector cell activating signals and lower ability to trigger effector functions. IgA is the predominant isotype in mucosal surfaces and in secretions, and its neutralizing capacity is crucial for protecting mucosal surfaces from toxins, viruses, and bacteria. It has a low capacity to activate complement but can engage neutrophils and trigger strong ADCC. IgE antibodies are usually associated with hypersensitivity and allergic reactions as well as responses to parasitic worm infections. IgE can trigger ADC and ADCP as well as being able to facilitate antigen presentation and, in the context of cancer immune surveillance, being able to repolarize pro-tumour macrophages into pro-inflammatory, anti-tumour phenotypes [2]. In addition to antibody isotypes, another feature that can influence antibody effector function is antibody glycosylation, which might modulate Fc receptors’ affinity and consequently antibody effector function. This has been widely studied for IgG isotypes, with interesting findings on the effects of fucosylation, galactosylation, and sialylation [3]. Of notice, alterations in IgG galactosylation have been reported as a biomarker for multiple cancer types [4]. Antibodies can also have a direct effect by binding to the target antigen. For cell surface antigens involved in downstream signalling, antibody-target engagement can sometimes have an agonistic effect on the target which could result in activation of a signalling cascade, but most often the binding of the antibody could have an antagonistic/inhibitory effect on the target’s downstream signalling functions. This can result in impaired cell growth and apoptosis; for cell surface antigens involved in cell–cell interactions or adhesion, antibody binding could impair or prevent these processes resulting in inhibition of tumour progression (Fig. 1) [1].

It has been suggested that the humoral immune system plays an important role in both the support and suppression of carcinogenesis [5]. For instance, several studies have reported the ability of B cells to inhibit tumour development through the production of tumour-reactive antibodies [6]. However, B cells can also contribute to immune tolerance and allow tumour development by producing immunosuppressive cytokines and antibodies which are ineffective in mediating immune effector functions [6]. Moreover, the humoral immune system is crucial for protection against invading pathogens and plays a critical role in the control and suppression of malignant cells via immunosurveillance. Therefore an imbalance in the immune system homeostasis may have an effect in carcinogenesis. There is ample evidence linking prior and chronic exposure to several infectious agents with a higher risk of cancer (i.e. human papillomavirus (HPV), Epstein-Barr virus (EBV), and Helicobacter pylori (HP)). Moreover, epidemiological evidence has pointed to significant associations between autoimmune disorders and cancer risk. An increased risk of malignancies has been observed previously in different autoimmune disorders.

Furthermore, immunoglobulins against self-antigens and tumour-associated antigens (TAAs) have been found both in the serum of patients with cancer and in the tumour microenvironment [7, 8]. Tumours can produce TAAs either by mutational mechanisms (mutated tumour-specific antigens, mTSAs) or by non-mutational mechanisms (non-mutational TAAs, nmTAAs), which could be overexpressed in cancer compared to normal tissue or may be cancer-specific. TAAs may induce an immune response. Humoral immune surveillance mechanisms may be protective against tumour cells and inhibit cancer growth, however, if the antigens are not tumour specific, the immune system can also recognize antigen-expressing non-malignant cells resulting in autoimmune reactions [7, 9, 10]. However, the propensity of tumour cells to escape immune surveillance may be a key step in tumorigenesis [6].

The presence, specificity, and isotype distribution of Igs in patients with cancer likely have an impact on tumour progression and could potentially inform on early detection of cancer and even predict the survival of the patient [6, 11]. Procedures to test the presence of antibodies, especially serum antibodies, are minimally invasive and easy to measure, and for this they harbour potential as biomarkers for cancer. Therefore, evaluating the link between antibodies and cancer risk and validating antibodies as biomarkers for diagnostic purposes are crucial. This may be especially beneficial in relation to cancers for which screening tests are currently lacking, but for which earlier detection would provide a substantial chance to treat promptly and offers a better chance of prolonged survival. In the present study, we aimed to outline the current evidence for the associations between the most researched immunoglobulin types and the risk of tissue site-specific cancers, and for the utility of Igs as biomarkers for cancer detection.

Methods

Data sources and searches

The current systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [12]. We performed
Figure 1: (A) Schematic representing antibody structure with heavy and light chains, and Fab, hinge, and Fc regions. (B) Heavy chain constant regions of different isotype are labelled in: light blue (IgD), yellow (IgG), blue (IgE), pink (IgA), red (IgM); IgM and IgA J chain is in blue. (C) Antibody-mediated anti-tumour or pro-tumour effector functions. Antibodies can exert several anti-tumour effector functions: mediating ADCC, ADCP, and CDC. Antibodies engaged with FcRs on immune effector cells and bound to tumour-derived antigens to form immune complexes, can (a) repolarize immune cells such
a literature search of epidemiological studies using PubMed with the search terms presented in Table 1. We included human studies published in English between 1 January 2000 and 9 September 2021. After preliminary screening of titles and abstracts, five independent reviewers (MM, NL, KB, SC, and AS) assessed the full text and reference lists of relevant publications for final inclusion; articles cited as references that were considered to be potentially relevant were also reviewed.

Study selection

Only epidemiological studies looking at the association between any serum immunoglobulin antibodies and cancer risk were included. No publications exploring antibodies as potential markers of cancer survival or cancer prognosis were included. We also excluded publications using immunoglobulins as molecular markers in experimental studies such as imaging techniques and/or treatments.

The inclusion criteria considered studies on adults only. Single case studies were excluded. No other restrictions were placed on publication type, with all systematic reviews, narrative reviews, meta-analyses, original research articles (experimental, observational, and clinical trials), commentaries, letters, and editorials identified in the PubMed search, being considered eligible. Non-English publications, duplicate studies, preprints, errata, and animal studies were excluded. Moreover, only publications with full text available were included.

For each selected study, the following study characteristics were extracted into a designated datasheet: name of the first author, year of publication, study location, study design, number of participants, exposure, outcome (i.e. cancer type), main findings, and other observations.

Results

Figure 2 shows the PRISMA flowchart illustrating the study selection procedure. Our PubMed search resulted in a total of 2126 studies. A full-text review was undertaken on 425 potentially eligible articles after title and abstract screening. Following full-text review, 273 publications were included. Of the 152 full-text articles excluded, 2 were looking at paediatric populations, 56 explored a different outcome (i.e. not cancer risk), 90 investigated a different exposure (i.e. antibodies), and 3 were repeated studies. Moreover, information on publications referenced in Tables 2–6 can be found in Supplementary Table S1.

We observed three main categories in the publications, namely, serum immunoglobulins (n = 34), infectious agent-associated immunoglobulins (n = 158), and tumour and self-antigen reacting antibodies (n = 81). Therefore, the systematic review is structured following these main groupings. An overview of the main antibodies identified in the current review is illustrated in Fig. 3.

Immunoglobulin M, G, A, and E

We identified 34 papers that assessed the risk of cancer in relation to the different immunoglobulin isotypes: IgE (n = 15), IgA (n = 7), IgG (n = 6), and IgM (n = 6). All studies followed an observational type of study design (case-control or cross-sectional designs). No clinical trials were identified. Most studies investigated the general population, except for three papers exploring IgM in patients with cirrhosis, and one exploring patients with IgG4-related diseases (IgG4-RD). An overview of the main findings is given in Table 2.
Immunoglobulin M (IgM)

Six studies were found looking into the association between IgM levels and the risk of cancer. One study reported an increased risk of chronic lymphocytic leukaemia in patients with increased levels of IgM [13]. No associations were found with other cancer types (i.e. overall, pancreatic, melanoma, bladder, and hepatocellular carcinoma) [14–16].

Immunoglobulin G (IgG)

Six studies have looked into the link between serum IgG levels and risk of site-specific cancer, however, not many studies explored the association with overall cancer. One cohort study found no association between serum IgG and overall cancer risk [17]. When looking at site-specific cancers, a large cohort study reported a negative association between serum IgG and risk of pancreatic cancer [16]. No associations were found for other cancer types (i.e. melanoma, bladder) [5, 14, 15]. Furthermore, a study focused on the association between IgG4-related disease (IgG4-RD), an inflammatory condition, and the risk of numerous cancer types. This observational study reported that the patients with IgG4-RD disease were at higher risk of overall cancer and lymphoma [18].

Immunoglobulin A (IgA)

Epidemiological studies have reported an inconsistent relationship between IgA levels and the risk of cancer [19, 20]. A meta-analysis of 14 studies found a strong positive association with solid cancers [5]. However, a strong negative association was also found between IgA and the risk of gastrointestinal cancer and lymphoma [19]. Moreover, no significant associations were found in various studies looking at overall, pancreatic, melanoma, and bladder cancer risk, in relation to IgA levels [14–16].

Immunoglobulin E (IgE)

Atopy and allergies are defined by exaggerated IgE responses to environmental allergens. We found 12 studies looking at the association between overall IgE (total concentration of IgE in serum) and the risk of various cancer types. Two cohort studies looking at total serum IgE reported a negative association with overall risk of cancer while two large cohorts found no significant associations with overall cancer risk [21, 22]. Moreover, four large cohort studies, including two with data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, found that IgE-deficiency and ultra-low IgE levels were strongly associated with an increased risk of overall cancer [23–25]. One of these studies reported a strong positive association between low levels of serum IgE and the risk of chronic lymphocytic leukaemia, lymphomas, and multiple myeloma [25]. On the other hand, a large case-control study reported a strong positive association between IgE and head and neck cancers [26]. No other significant associations were found with other cancer types (i.e. pancreatic, prostate) [27].

Several studies have investigated the association between self-reported allergies and allergen-specific IgE, with varying results. A cohort study reported a positive association between serum allergen-specific IgE and risk of prostate cancer [28]. Moreover, a population-based case-control study found an increased risk of squamous cell carcinoma of the skin in patients with high levels of allergen-specific IgE [29]. On the other hand, a nested case-control from the EPIC cohort found a strong negative association between allergen-specific IgE and risk of glioma [30]. No associations were found between this allergen-specific IgE and overall and other specific cancer types (i.e. lung, breast, lymphoma, colon and rectum, pancreatic) [22, 28, 31]. When looking at asthma-specific IgE, a strong positive association was found with lung cancer [32]. On the other hand, a pooled analysis of 13 case-control studies found a negative association between asthma-specific IgE or self-reported food allergies, and risk of non-Hodgkin lymphoma [33]. No associations were found with other cancers (i.e. overall, breast, prostate, and pancreatic) [32].

Cancer-promoting infectious agents

We identified 158 studies assessing the risk of cancer in relation to different antibodies against various infectious agents. All studies followed an observational type of study design. No clinical trials were identified. The most commonly described associations were for antibodies against Epstein–Barr Virus (n = 25), hepatitis B virus (HBV, n = 15), hepatitis C virus (HCV, n = 14), human papillomavirus (n = 29), H. pylori (n = 29), and chlamydia trachomatis (n = 6). No consistent associations were found with the other infectious agents. An overview of the main findings is given in Table 3.

Epstein–Barr virus

Antibodies against four major EBV antigens (viral capsid antigen (anti-VCA) IgA, IgM and IgG, early antigen (anti-EA) IgG, EBV nuclear antigen (EBNA), and ZEBRA IgM) have been studied in association with the risk of various cancers. Several studies looking into the association between EBV immunoglobulins and nasopharyngeal carcinomas (NPC) have found a positive association with all EBV antigens. For instance, a cohort study found that anti-EBNA1 neutralizing antibodies may be a sensitive biomarker for risk of NPC.
This was supported by 2 other population-based studies [35, 36]. Moreover, a large cohort looking at anti-VCA IgA found a strong positive association with the risk of NPC [37]. These results were also supported by two other cohort studies [38, 39]. Of the five studies that examined the risk of gastric cancer (GC), two epidemiological studies reported an increased risk of GC in patients with positive anti-VCA IgG [40, 41]. However, no significant associations were found between anti-EA antibodies and risk of GC [42]. One case-control study with 321 cases of ovarian cancer reported a positive association with anti-EBV IgG, however, no association was found for anti-EBV IgA [43]. No significant associations have been reported between EBV antibodies and the risk of lymphoma and breast cancer [44].

Hepatitis B virus
Antibodies against hepatitis B virus antigens (hepatitis core antigen (anti-HBc) IgG, hepatitis B specific antigen (anti-HBs) IgG and IgM, and anti-hBe IgM) have long been suspected to be predictive factors for hepatocellular carcinoma (HCC). A consistent positive association was found between patients with HBsAg seropositive and risk of HCC [45]. In addition, three large cohort studies reported a stronger positive association in patients who were seropositive both anti-HBs and HBsAg compared with that seropositive for HBsAg [46]. Moreover, two population-based cohort studies found a positive association between positive anti-HBe antibodies and the risk of HCC [47, 48]. In contrast, a large cohort from a hepatitis B-endemic area found no significant association between patients with detected serum anti-HBs IgG and risk of HCC [49]. Furthermore, two case-control studies looking at anti-HCV, HBsAg, anti-HBc, and anti-HBs antibody positivity reported an increased risk of pancreatic cancer [50, 51]. No other associations were found between HBV antibodies and the risk of head and neck cancer and biliary tract cancer [52, 53].

Hepatitis C virus
Several studies have investigated the relationship between hepatitis C virus antibodies and the risk of hepatocellular carcinoma. A case-control study found a strongly increased risk of HCC in patients with positive anti-HCV antibody seropositivity [54]. This positive association was supported by three other epidemiological studies [55–57]. Additionally, a cohort also analyzing HBV antibodies found a higher risk of HCC in individuals who were seropositive for antibodies to both HCV and HBV [53]. Moreover, three epidemiological studies looking into the association between HCV antibodies and lymphomas found no significant associations [58–60]. Lastly, a case-control from Japan reported a positive association between anti-HCV antibodies and the risk of intrahepatic cholangiocarcinoma [61].

Human papillomavirus
High risk (16 and 18) human papillomavirus antibodies have frequently been linked with cervical and other anogenital cancers (i.e. anus, vulvar, vaginal, and penile). Several epidemiological studies showed that serum antibodies to HPV 16 and 18 are associated with an increased risk of cervical cancer [62, 63]. Moreover, no consistent associations were found between other anogenital cancers and anti-HPV antibodies. Numerous studies investigating the relationship between HPV antibodies and head and neck cancers have found consistently positive associations between positive HPV 16 antibodies and the risk of head and neck cancers [64, 65]. No significant associations were found for other HPV types [64]. Furthermore, two large case-control studies from Sweden and Norway reported an increased risk of non-melanoma skin cancer in patients with detected antibodies for both HPV 16 and 18 [66, 67]. Lastly, no significant associations were found between HPV antibodies and the risk of prostate and lung cancer [68].
Table 2: Summary of results of associations between immunoglobulin isotypes and site-specific cancer risks. The strength of association is defined by the number of studies reporting on the association, the range of the hazard ratio/odds ratio/relative risks/standardized incidence ratio reported in each study, and the statistical significance.

| Exposure                          | Population                  | Outcome                  | Number of studies | Main findings                |
|----------------------------------|-----------------------------|--------------------------|-------------------|-----------------------------|
| Total IgE                        | IgE deficiency              | General population       | Overall           | Strong negative association |
|                                  |                             |                          | 2                 |                             |
|                                  | High total IgE              |                          | Overall           | Intermediate positive association |
|                                  |                             |                          | 4                 |                             |
|                                  | Lymphoma, leukaemia,        |                          | 2                 | Strong positive association |
|                                  | myeloma                     |                          |                   |                             |
|                                  | Prostate (high PSA)         |                          | 1                 | Weak positive association   |
|                                  | Head and neck               |                          | 1                 | Intermediate positive association |
|                                  | Skin cancer                 |                          | 1                 | No significant association  |
| High allergen-specific IgE (serum) | Lung                        |                          | 1                 | No significant association  |
|                                  | Breast                      |                          | 2                 | No significant association  |
|                                  | Prostate                    |                          | 1                 | Intermediate positive association |
|                                  | Lymphoma                    |                          | 1                 | No significant association  |
|                                  | Colon, rectum               |                          | 1                 | No significant association  |
|                                  | Brain (Glioma)              |                          | 1                 | Intermediate negative association |
|                                  | Pancreatic                  |                          | 1                 | No significant association  |
|                                  | Skin cancer                 |                          | 1                 | Intermediate positive association |
|                                  | Lung cancer                 |                          | 1                 | No significant association  |
|                                  | Breast                      |                          | 1                 | No significant association  |
|                                  | Prostate                    |                          | 1                 | Intermediate positive association |
|                                  | Lymphoma                    |                          | 1                 | Strong negative association |
|                                  | (pooled analysis of 13 studies) |                  |                   |                             |
| Self-reported allergies          | Lung cancer                 |                          | 1                 | Intermediate negative association |
|                                  | Breast                      |                          | 1                 | No significant association  |
|                                  | Prostate                    |                          | 1                 | No significant association  |
|                                  | Lymphoma                    |                          | 1                 | Strong negative association |
|                                  | (pooled analysis of 13 studies) |                  |                   |                             |
| IgA                              | High total IgA              | General population       | Overall           | No significant association|
|                                  |                             |                          | 3                 |                             |
|                                  | Pancreatic                  |                          | 1                 | No significant association  |
|                                  | Melanoma                    |                          | 1                 | No significant association  |
|                                  | Bladder                     |                          | 1                 | No significant association  |
|                                  | Solid cancers               |                          | 1                 | Strong positive association |
|                                  | Lymphoma                    |                          | 2                 | Strong negative association |
|                                  | Gastrointestinal            |                          | 2                 | Strong negative association |
|                                  |                               |                          |                   |                             |
| IgG                              | High total IgG              | General population       | Overall           | No significant association|
|                                  |                             |                          | 1                 |                             |
|                                  | Pancreatic                  |                          | 1                 | No significant association  |
|                                  | Melanoma                    |                          | 1                 | No significant association  |
|                                  | Bladder                     |                          | 1                 | No significant association  |
|                                  | Solid cancers               |                          | 1                 | No significant association  |
|                                  | Lymphoma                    |                          | 2                 | Strong negative association |
|                                  | Gastrointestinal            |                          | 2                 | Strong negative association |
|                                  |                               |                          |                   |                             |
| IgM                              | High total IgM              | General population       | Overall           | No significant association|
|                                  |                             |                          | 1                 |                             |
|                                  | Pancreatic                  |                          | 1                 | No significant association  |
Chlamydia trachomatis

Antibodies against chlamydia trachomatis have most commonly been associated with the risk of cancers of the reproductive system (i.e., ovarian, cervical, and prostate). A recent study using data from the EPIC cohort reported an increased risk of ovarian cancer in patients seropositive for antibodies recognizing chlamydia trachomatis [69]. A case-control found a positive association between high titers of antibodies against chlamydia trachomatis and cervical cancer; however, another large population-based case-control study found no significant associations [70]. Lastly, a case-control study with 38 incident cases of prostate cancer reported a protective effect in patients seropositive for chlamydia trachomatis antibodies [71].

Helicobacter pylori

Most studies have focused on the association between H. pylori and the risk of gastric cancer. A recent cohort of 19,106 Japanese men reported an increased risk of GC for patients with undetectable anti-H. pylori IgG titers. However, the increase in risk was dependent on the severity of atrophic gastritis, resulting from persistent H. pylori infection [72]. This was supported by a cross-sectional study that found that serum IgG1 against H. pylori was significantly lower in subjects with GC (n = 62) [73]. On the other hand, a case-control study including 225 incident GC cases and 435 controls reported an increased risk of GC in individuals with elevated titers of IgA and IgG serum antibodies for H. pylori [74]. This positive association between immunoglobulin and risk of GC has been supported by the majority of epidemiological evidence to date [66–77]. Moreover, three epidemiological studies were identified looking at the association between antibodies against H. pylori and risk of colorectal cancer (CRC). However, no significant associations were found [78].

Tumour and self-reactive antibodies

A total of 81 papers were identified assessing the risk of cancer in relation to tumour or self-reactive antibodies. Of the identified papers, 35 studies specifically addressed the risk of any cancer or specific types of cancers in the general population. A further 23 studies were directed towards specific ‘at risk’ populations, such as carriers of mutations in BRCA1/2, or those with thyroid nodules, while another 23 addressed the risk of cancer in relation to various autoantibodies associated with autoimmune diseases within specific patient cohorts. An overview of the main findings from this section is given in Tables 4–6.

Regarding the target antigens for the autoantibodies evaluated in the general population (Table 4), studies generally showed positive associations for single-antigen targets such as p53, New5Gc, IGFBP-2, BARD1, CD25, FoxP3, MUC1, CA125, SBP1, and HE4, albeit with relatively low sensitivity [79–87]. The remaining 13 studies investigated the general population to assess cancer risk in relation to serum antibodies against multiple antigens, either to identify the most immunogenic of these or to develop and evaluate a panel of biomarkers for diagnostic or screening purposes. These studies indicate strong positive associations for multiple antibodies, with most indicating relatively high specificity and sensitivity for specific antibody panels against tumour specific and self-antigens [88]. For example, Zhang et al. reported a panel of nine candidate autoantibody markers that achieved 94.3% sensitivity and 90.4% specificity for detecting mesothelioma [89]. Similarly, a panel comprising antibodies to the autoantigens, p53, c-myc, human epidermal growth factor receptor 2 (HER2), New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO-1), cancer/testis antigen gene (CAGE), Mucin 1 (MUC1), and GBU4-5, achieved high sensitivity and specificity for the detection of squamous cell lung cancers [90].

Studies performed within specific target populations included populations at high cancer risk (e.g. BRCA mutation carriers, populations identified with high risk of oesophageal cancer for screening), cohorts with specific organ disease populations (e.g. lung and thyroid disease, and populations with autoimmune or paraneoplastic syndromes, including autoimmune myopathies, scleroderma, Sjögren syndrome, autoimmune thyroiditis, autoimmune vasculitis, and autoimmune phemphoid) (Tables 5 and 6). The most consistent positive associations were seen for the association between overall cancer risk in scleroderma patients with anti-RNA polymerase-3 (RNAP-3) antibodies and for thyroid cancer among people with autoimmune thyroiditis who had high anti-thyroglobulin (Tg) serum antibody titres [91, 92]. Among people undergoing thyroidectomy for any reason, thyroid cancer risk was also associated with the presence of anti-Tg antibodies, though the evidence was mixed regarding anti-thyroid peroxidase (TPO) seropositive status [93]. Antibody panels applied in high-risk populations again appeared to have relatively high sensitivity and specificity in relation to identifying patients with cancer or individuals with premalignant disease [8].

Discussion

There is a growing body of evidence linking antibodies to cancer risk, especially for specific immunoglobulin isotypes and for both TAA-reactive and self-reactive antibodies. B cells
Table 3: Summary of results of associations between infection-related immunoglobulins with site-specific cancer risks. The strength of association is defined by the number of studies reporting on the association, the range of the hazard ratio/odds ratio/relative risks/standardized incidence ratio reported in each study, and the statistical significance.

| Exposure | Antigen/Immunoglobulin | Outcome | Main findings |
|----------|------------------------|---------|--------------|
| EBV (IgG, IgM and IgA) | VCA | Gastric cancer | Intermediate positive association |
| | EBNA | | No significant associations |
| | ZEBRA | | No significant associations |
| | EA | | No significant associations |
| | EBNA | Nasopharyngeal carcinoma | Very strong positive association |
| | VCA | | Very strong positive association |
| | EA | | Weak positive association |
| | Gp350 | | Weak positive association |
| | VCA | Breast cancer | No significant association |
| | EBNA | | No significant association |
| | VCA | Lymphoma (all) | No significant association |
| | EBNA | | No significant association |
| | EA | | No significant association |
| | VCA | Ovarian cancer | Moderately positive association |
| Hepatitis B virus | Anti-HBs (IgG and IgM) | Hepatocellular carcinoma | Very strong positive association |
| | Anti-HBc (IgM) | | Strong positive association |
| | Anti-HBc (IgG) | | Strong positive association |
| | Anti-HBs (IgG and IgM) | Pancreatic cancer | Strong positive association |
| | Anti-HBc (IgM) | | Weak positive association |
| | Anti-HBs (IgG and IgM) | Extrahepatic bile duct cancer | Weak positive association |
| | Anti-HBc (IgM) | Oropharyngeal | Weak positive association |
| Hepatitis C virus (IgM) | Anti-HCV | Hepatocellular carcinoma | Very strong positive association |
| | Anti-HCV | Pancreatic cancer | No significant association |
| | Anti-HCV | Lymphoma (all) | No significant associations |
| | Anti-HCV | Renal | Weak positive association |
| | Anti-HCV | Cholangiocarcinoma | Weak positive association |
| HPV (IgG) | 16 | Overall cancer | No significant association |
| | 16 | Oesophageal cancer | No significant association |
| | 18 | | No significant associations |
| | 6 | Oropharyngeal cancer | Strong positive association |
| | 11 | | No significant associations |
| | 16 | | No significant association |
| | 18 | | Weak positive association |
| | 16 | Lung cancer | No significant associations |
| | 5 | Non-melanoma skin cancer | No significant associations |
| | 6 | | No significant associations |
| | 8 | | No significant associations |
| | 16 | | Intermediate positive association |
| | 18 | | Intermediate positive association |
| | 16 | Cervical cancer | Very strong positive association |
| | 18 | | No significant association |
| | 16 | Prostate cancer | No significant association |
| | 18 | | No significant association |
| | 33 | | No significant association |
| | 16 | Anogenital cancers (anus, vulvar, vaginal, penile) | Strong positive association |
| | 18 | Anogenital cancers (anus, vulvar, vaginal, penile) | Strong positive association |
| C. Trachomatis (IgG) | Ovarian cancer | | Strong positive association |
| | Cervical cancer | | No significant associations |
| | Prostate cancer | | Low negative association |
| H. Pylori | IgG | Gastric cancer | Intermediate positive association |
can suppress tumour growth by producing antibodies able to facilitate CDC and antigen presentation or engage effector cells to mediate ADCC and ADCP; however, have shown the ability to also support tumour growth by expressing antibodies with poor ability to mediate the above anti-tumour responses, such as isotypes like IgG2 and IgG4 [6]. Antibodies have great potential as biomarkers for cancer since procedures to test for their presence are minimally invasive and antibodies are fairly stable and easy to measure \textit{ex vivo}. Research identifying antibodies that might be appropriate biomarkers for early detection of cancer, based on our systematic review, still appears to be an emerging field. Most of the studies reviewed were observational, and largely attempted to identify potential markers in association with cancer. Few of the studies test the predictive potential of antibodies to detect an overall cancer risk or risk for site-specific cancers, specifically for one or more autoantibodies (autoantibody panels). Larger studies are required to validate these antibodies as cancer biomarkers and to apply them in clinical practice. The current systematic review presents a broad landscape of potential biomarkers for early diagnosis of cancer, and our findings highlight the importance of this newly emerging research topic in cancer biomarker discovery.

A consistent association between serum levels of certain immunoglobulin isotypes and risk for certain cancers was found. However, studies have been conducted in several methods and in different settings and have reported diverse results. It is therefore difficult to point to antibody class-specific associations with cancer risk. While no association was found between general IgG and IgM levels, several studies we found report associations between altered serum levels of IgE and cancer risk [13, 15, 19, 21, 22]. Some studies report that high titres of allergen-specific IgE are associated with an increased risk of prostate cancer and squamous cell carcinoma, and conversely these show a negative association with glioma incidence [29, 30]. Low IgE titres have also been associated with a high risk of overall cancer and an increased risk of haematological malignancies [25]. High IgA titres have been found associated with the risk of a range of solid tumours, but have a strong negative association with risk of gastrointestinal cancer and lymphoma diagnosis, while other studies show no significant associations with overall, pancreatic, melanoma, and bladder cancer risk, in relation to IgA levels [19, 20].

Different types of cancers have different aetiology. This might explain the controversial results on different effects of IgE and IgA antibody titres on different types of cancers [19, 24]. IgE can exert anti-tumour functions, but can be also associated with systemic chronic inflammation, which can instead promote tumourigenesis [21]. This could explain the association between low serum levels of IgE and increased cancer risk for cancers located far from the site of inflammation. On the other hand, high IgE levels as part of the local chronic inflammatory milieu could predispose to cancers developing at that site of inflammation; for example lung cancer in patients with asthma and non-melanoma skin

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Exposure & Antigen/ Immunoglobulin & Outcome & Main findings \\
\hline
\hline
IgA &  & Pancreatic cancer & Strong positive association \\
CagA &  & Colorectal carcinoma & Intermediate positive association \\
VacA &  & Lymphoma & No significant association \\
CagA &  & Prostate cancer & No significant associations \\
CagA & Anti-H. Pylori & Oropharyngeal carcinoma & Weak positive association \\
Herpes simplex virus 2 (IgG) &  & Cervical cancer & No significant associations \\
Herpes simplex virus 1 &  & Prostate cancer & No significant associations \\
Human herpes virus -8 &  & Non-Hodgkin Lymphoma & No significant associations \\
(Kaposi sarcoma) &  & Glioma & Weak negative association \\
Varicella zoster virus &  & Prostate cancer & No significant associations \\
T. vaginalis &  & Gastrointestinal cancer & No significant associations \\
CMV & Anti-CMV & Breast cancer & No significant associations \\
MCV & Anti-MCV & Merkel cell carcinoma & Weak positive association \\
BKV &  & Bladder cancer & Weak positive association \\
JCV &  & Bladder cancer & Weak positive association \\
Porphyromonas gingivalis &  & Colorectal cancer & No significant associations \\
Chlamydia pneumoniae & IgA & Pancreatic cancer & Weak positive association \\
Polyomavirus & Anti-polyomavirus & Oropharyngeal cancer & Weak positive association \\
GBV & Anti-GBV & Non-Hodgkin lymphoma & No significant association \\
Propionibacterium Acnes &  & Prostate cancer & Intermediate positive association \\
\hline
\end{tabular}
\caption{Continued}
\end{table}

VCA, viral capsid antigen; EA, early antigen; HBs, hepatitis B specific antigen; HBc, hepatitis B core antigen; \textbackslash
Table 4: Summary of results of associations between tumour and self-reactive antibodies and site-specific cancer risk, in the general population.

The evidence of association is defined by the number of studies reporting on the association, the range of the hazard ratio/odds ratio/relative risks/standardized incidence ratio reported in each study, and the statistical significance.

| Cancer type       | Serum Antibodies                                      | Main findings                                         | Diagnostic potential                           |
|-------------------|-------------------------------------------------------|-------------------------------------------------------|------------------------------------------------|
| All/any           | Anti-p53                                              | Positive association                                  | NA                                             |
|                   | Anti-phospholipid                                     | Possible inverse association                           | NA                                             |
| Breast            | Antibodies to six autoantigens: p53, c-myc, HER2, NY-ESO-1, BRCA2 and MUC1 (assessed individually) | Positive association for the presence of 1 or more of listed autoantibodies | Autoantibody panel likely to perform better than single marker – but not assessed |
|                   | Anti-thyroid peroxidase                               | Inverse association                                   | NA                                             |
|                   | Anti-p53                                              | Positive association                                   | NA                                             |
|                   | Anti-Neu5Gc (antibodies to meat-derived antigens)     | Positive association for total anti-Neu5Gc IgG; Single epitope no association | NA                                             |
|                   | IGFBP-2 IgG                                           | Positive association                                   | AUC = 0.92 (when combined with serum IGFBP-2 levels) |
|                   | Multiple TAA antibodies (8000 potential antigens)     | Positive association: MAPKAPK3, PIM1, STK4, SRC, and FGFR4 Negative association: ACVR2B | Specificity and sensitivity high for anti-ACVR2B, anti-MAPKAPK3, anti-PIM1 combined |
| Oesophageal       | Anti-ASXL2*                                           | Positive association                                   | AUC = 0.67                                      |
|                   | Anti-ASXL2*                                           | Positive association                                   | AUC = 0.76                                      |
|                   | Anti-p53                                              | Positive association                                   | NA                                             |
| Gastric           | Panel; p62, c-Myc, NPM1, 14-3-3ζ, MDM2 and p16        | Positive associations                                  | Selected six panel for testing                 |
| Glioma            | Anti-IGFBP-2                                          | Positive association for astrocytoma                   | AUC = 0.80 (when combined with serum IGFBP-2 levels) |
| Hepatocellular cancer | Multiple TAA antibodies                                   | Positive associations for autoantibodies to calretulin, cytokeratin 8, nucleoside diphosphate kinase A, F1-ATP synthase | NA                                             |
|                   | Multiple antibodies                                   | Positive association for antibodies to 21 TAAs; (best performers: IMP-1, KOC, p53 and c-myc, Sui1 and RalA, Calreticulin, and HCC1) | Moderate sensitivity high specificity          |
|                   | 12 antibody panel                                      | Positive association for autoantibodies to HCC1, P16, P53, P90, and Survivin | NA                                             |
| Lung cancer/NSCLC | Panel: p62, BIRC, Livin-1, p53, PRDX, NY-ESO-1 and Ubiquitin | Positive association                                  | AUC = 0.81                                      |
|                   | Panel: p53, c-myc, HER2, NY-ESO-1, CAGE, MUC1 ans GBU4-5 | Positive association                                  | High sensitivity for squamous cell lung cancer, moderate sensitivity for all lung cancers |
|                   | Panel: GAGE7, CAGE, MAGA1, SOX2, GBU4-5, PGP9.5, and p53 | Positive association                                  | Moderate sensitivity and specificity           |
|                   | Multiple antibodies: (212 selected from immunogenic tumour expressed proteins) | Positive association for the 5 most immunogenic combined | High sensitivity and specificity               |
|                   | Multiple autoantibodies: p62, p16, Koc, p53, Cyclin B1, Cyclin E, Survivin, HCC1, and RalA | Strongest serological response: Survivin, Cyclin B1, HCC1, and p53 | Low to moderate potential as individual autoantibodies |
|                   | Anti-BARD1                                            | Positive association                                  | High sensitivity and specificity               |
|                   | Brain protein autoantibodies CD25 and FoxP3 IgGs      | Positive association                                  | NA                                             |
| Mesothelioma      | Panel including PDIA6, MEG3, SDCCAG3, IGHG3, IGHG1    | Positive association                                  | High specificity and sensitivity               |
|                   | Anti-p53                                              | No association                                        | NA                                             |
| Lymphoma/NHL      | Anti-cyclic citrullinated peptide (CCP)               | No association                                        | NA                                             |
IgA may have a protective role in certain tissues such as mucosal areas and the gastrointestinal tract, which would explain the strong negative correlation between high IgA levels and positive associations with the development of gastrointestinal cancer [14, 19]. However, IgA can be associated with specific B cell subsets and their regulatory functions, such as the production of immunosuppressive cytokines like IL-10, which can support a pro-tumour microenvironment [19]. Together, these studies may suggest the importance of considering the inflammatory environment in disparate anatomical sites and its relation to the nature of the humoral response and how this might relate to carcinogenesis.

With the exception of antibodies against EBV which have shown a positive association with NPCs, and possibly with gastric and ovarian cancers, most studies focused on investigating the association between the presence of antivirus or antibacteria antibodies and cancer risk, report a positive association with specific cancers known to be associated to that specific virus/bacterial infection site (for instance, HBV and HCV with hepatocellular carcinoma, HPV with anogenital cancers), but no association with other cancers.

### Table 4. Continued

| Cancer type | Serum Antibodies | Main findings | Diagnostic potential |
|-------------|------------------|---------------|----------------------|
| Ovarian cancer | Panel: anti-MDM2, PLAT, NPM1, 14-3-3 Zeta, p53, and RalA | Positive association | High specificity and sensitivity |
| Anti-MUC1, anti-CA125 | Positive association | NA |
| Anti-MUC1 | Indirect evidence for inverse association | NA |
| Anti-p53 and anti-SBP-1** | Positive association for serous ovarian cancer | High specificity and sensitivity for CA125, anti-TP53, and anti-SBP1 combined (AUC 0.96) |
| Anti-HE4 | Positive association | NA |
| Pancreatic | Anti-Ezrin | No association | NA |
| Bladder | Anti-UPII | Positive association | NA |

### Table 5

| Target Population | Cancer risk | Serum antibody | Main findings | Diagnostic potential |
|-------------------|-------------|----------------|---------------|----------------------|
| High risk (BRCA) carriers | Breast cancer | MUC1 IgG | No association | NA |
| High risk oesophageal cancer (screening) population | Oesophageal cancer | Panel of eight autoantibodies: p53, IMP1, P16, cyclin B1, P62, c-myc, Survivin and Koc NY-ESO-1 STIP1 | Positive association | High specificity and moderate sensitivity |
| Lung disease | Premalignant lung lesions | Panel of nine autoantibodies | Positive association | Moderate specificity and moderate sensitivity for premalignancy |
| Endometrial cancer patients | Endometrial cancer | Anti-p53 | Positive association for serous histology | NA |
| Ovarian cancer patients | Ovarian cancer | NY-ESO-1 | 48% seropositive | NA |
| Thyroid disease: (patients having nodule FNAB or thyroidectomy) | Thyroid cancer (papillary carcinoma) | Anti-Tg | Positive association | High specificity and low sensitivity (ref 80) |
| | | Anti-TPO | No association | NA |
| | | Autoimmune thyroiditis (either Tg or TPO Ab +ve) | No association | NA |

Note: The evidence of association is defined by the number of studies reporting on the association, the range of the hazard ratio/odds ratio/relative risks/standardized incidence ratio reported in each study, and the statistical significance.

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Testing the presence of specific anti-viral or antibacterial antibodies is often the only method to assess if there is or there has been a specific infection, and it is therefore difficult to distinguish whether it is the presence of the antibodies that is associated with cancer risk and not the virus/bacterial infection itself [72]. In addition, only one study relating to infectious agents described the presence of neutralizing antibodies (i.e. EBV) [34]. The presence of neutralizing antibodies implies that the humoral response generated is already protective against a pathogen, compared to an antibody response that recognizes the epitope but which still allows the pathogen to infect, survive, and replicate. Therefore, further studies looking into the association between neutralizing antibodies against various infectious agents in association to cancer risk are required.

The risk of cancer appeared to be increased among people who present with various autoimmune diseases (i.e. in most cases autoimmune diseases involve the body producing antibodies toward ‘self’ (autoantigens) which can lead to local or systemic inflammation and specific or systemic organ damage) [90, 93]. However, despite the increased risk of cancer, those with autoimmune diseases often have a better prognosis, leading to the hypotheses that such immune responses may be protective against the development of autoantigen-expressing cancer cells at an early stage of carcinogenesis, and therefore preventing cancer from developing and progressing [94]. Evidence of a better prognosis has been found for the development of vitiligo, denoting an immune attack on melanocytes, in patients with melanoma, and of thyroiditis in patients with thyroid cancer [10].

Several studies indicate a high risk of cancer diagnosis within 3 years of diagnosis of specific autoimmune diseases, specifically scleroderma and autoimmune myopathies, suggesting that some autoimmune pathologies may actually
Autoantibodies to one antigen have low sensitivity and/or specificity as biomarkers for individual cancer types, the development of panels of multiple autoantibodies may provide better sensitivity for cancer or specific cancer types.

This systematic review provides a comprehensive qualitative summary of the published epidemiological evidence of the associations between antibodies and the risk of overall and site-specific cancers. A large number of the cohort, case-control studies were included. However, given the broad subject and large amount of antibody types, in this study, we presented an overview of the most researched antibodies in relation to cancer risk, and it is possible that certain studies might have been missed in our literature review. Our systematic review thus presents a broad landscape of different antibodies with the potential of being identified and in the future validated as markers of early diagnosis of cancer. Larger observational studies and clinical trials are necessary to establish the potential prediction capability of such biomarkers or their combinations.

**Conclusion**

There is consistent evidence associating antibodies to cancer risk, especially for specific immunoglobulin isotypes and for both tumour-associated and self-reactive antibodies. However, research in this field is still in the early stages of development. No clinical trials assessing the utility of antibodies as biomarkers for screening or diagnostic assessment were identified, and most of the studies thus far have reported exploratory findings from observational studies, some involving modeling with validation cohorts with reports of specificity and sensitivity but which still require validation with larger cohorts. Therefore, larger studies and clinical trials are necessary to assess the efficacy of specific antibodies as markers for early cancer diagnosis.

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**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**Author contributions**

AS, MV, and SK conceived the study idea. MM performed the literature search. AS, MM, and KB developed the core criteria used in this study. AM, MM, KB, NL, and SC extracted the data from revised studies. AS, MM, KB, and SC wrote the first
Data availability

The data presented in this study are available on request from the corresponding author.

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