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Review

Increased plasma concentrations of tumour markers in the absence of neoplasia

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Abstract

Tumour markers are a very heterogeneous group of molecules that are generally found in very small concentrations in the plasma and serum of healthy individuals. In the process of neoplastic differentiation the cell can synthesize, release, or induce synthesis of other cells, thus increasing their concentration in plasma and serum. These substances may also increase their plasma concentration in patients without cancer due to processes that increase the release or reduce catabolism, and so give rise to false positives. An understanding of the main physiopathological processes that increase the concentrations of these substances could improve our interpretation of tumour markers and their clinical application. In this study we review the physiopathological processes that may increase the plasma concentrations of tumour markers. We performed a bibliography review in PubMed, searching for causes of false positives for the following tumour markers: α-Fetoprotein, CA 125, CA 15-3, CA 19-9, CA 72-4, carcinoembryonic antigen, CYFRA 21-1, squamous cell carcinoma, prostatic specific antigen, β_2-microglobulin, choriogonadotropin (β chain), chromogranin A, neuron specific enolase, HER2-neu, progastrin releasing peptide, S-100, and thyroglobulin. The results favour the use of tests which can identify pathological processes that may increase tumour marker concentrations.

Keywords: benign disease; false positives; tumour markers.

Introduction

Tumour markers are a very heterogeneous group of molecules that are generally found in very small concentrations in the plasma and serum of healthy individuals (1). In patients with cancer, their concentration[a] in plasma increases[b] for a variety of reasons, including greater cell exchange, release due to cell necrosis or the over-expression and secretion of certain proteins. In some cases, neoplastic cells even induce the synthesis of tumour markers by other cells. The concentration of tumour markers in plasma or in other biological fluids can be used in the screening, diagnosis and prognosis of cancer, even though their main semiologic value is in the follow-up of already diagnosed patients to monitor treatment and provide early diagnosis of tumour relapse (2).

In the absence of cancer, however, the values of tumour marker concentrations in plasma[a] may be above the upper reference limits established for presumably healthy individuals. Inflammatory processes or necrosis may release sufficient amounts of these substances for their concentrations to exceed the limits. Similarly, their concentration may increase due to a reduction in their catabolism brought about by a dysfunction in the organs responsible for eliminating them, such as the liver and kidneys.

The increase[b] in the concentration of a tumour marker above the discriminant value (normally the upper reference limit) in the absence of neoplasia is considered a false positive.

The different types of false positives can be classified as methodological, physiological or pathological. Methodological false positives are attributed to the measuring system; they arise due to the lack of specificity of the antibody, crossed reactions with other molecules, or due to the presence of heterophil antibodies. Increased values of some tumour markers have a physiological cause: for example, the

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[a] Unless specified otherwise, when we refer to ''the concentration of...'' or ''concentrations of…'' we mean the plasma concentration of the previously mentioned biological marker.
[b] In this article, the concept of ''increase'' or ''elevation'' in the concentration of a tumour marker in plasma is defined in relation to a previously established discriminant value or an upper biological reference limit.

CA 125 and CA 15-3 antigens in relation to the menstrual cycle. Finally, false positives with a pathological origin include alterations that increase marker release due to necrosis or inflammation, and the alterations that reduce its elimination (such as kidney or liver failure). False positives may also be brought about by the composition of the diet (excessive consumption of tea in the case of antigen CA 19-9), contamination of the sample (by saliva in the case of squamous cell carcinoma antigen) or any manoeuvres that increase the release of the tumour marker (for instance prostate massage in the case of prostate specific antigen).

In each tumour marker, false positive results may be due to a variety of causes. Table 1 shows most of the physiological and pathological conditions that can raise the concentration of tumour markers in the absence of cancer.

To interpret the result of the concentration of a tumour marker in a certain biological fluid, mainly plasma, physicians must be alert to the existence of these false positives. On the one hand, the values of certain biological values related to liver function (the concentration of aspartate-aminotransferase, alanine-aminotransferase, bilirubin, γ-glutamyltransferase) and on the other, values related to the kidney (concentration of creatinine, urea and either measured or calculated kidney glomerular filtration rate) may identify alterations in the catabolism of tumour markers. Some values related to pancreas function (the concentration of α-amylase and triacylglycerol-lipase) may be useful for identifying elevated tumour marker concentrations related to pancreatic diseases.

It is also necessary to determine tumour marker concentrations in these situations and the generally observed maximum values. Not all these magnitudes present the same increase in these diseases. For example, in the absence of cancer, the concentration of CA 19-9 antigen may present values 1000 times above the upper reference limit (3). In most cases, obviously, the increase is lower: for instance, it may be <5 times above the limit (4), or in unusual cases ten times above it (5).

The main reasons for elevated concentrations of various tumour markers in the absence of cancer are described below.

We carried out a bibliography review in PubMed searching between 1970 and 2010 for causes of false positives for tumour markers, and selected the most recent publications containing range, means and % of false positives, with the next key words: Tumour markers, APF, CA125, CA15-3, CA19-9 CA72-4 CEA, CYRRA 21-1 SCC, PSA, β_2-microglobulin, choriogonadotropin, chromogranin A, NSE, HER-2, ProGRP, S100, thyroglobulin, false positive, pulmonary benign disease, gastric benign disease, gynaecological benign disease, pancreatitis, hepatitis, benign liver disease, evaluation, increase concentrations, skin benign disease, brain damage.

There are certain factors that may affect the various measuring systems in a general way. In the case of an elevated tumour marker we may suspect the presence of heterophil antibodies due to the type of antibody used in the measurement. In some cases raised tumour markers have as been attributed to the presence of rheumatoid factor.

α-Fetoprotein

α-Fetoprotein (AFP) is a glycoprotein produced during fetogenesis, in the yolk sack, liver and gastrointestinal tract. In healthy pregnant women it may reach concentrations of 250 μg/L. After birth, these concentrations fall rapidly, with a half-life of 3–7 days (6). Concentrations of α-fetoprotein in neonates are very high. In addition, mean concentrations of 41,000 μg/L for this marker have been reported in cord blood (7), but during the first few months its values drop to the physiological values of adults, with a half-life of 3–8 days (8). The mean values are about 400,000 μg/L in babies born at 34 weeks of gestation whereas in those born at term the mean is 35,000 μg/L (9).

In adults, increased concentrations of α-fetoprotein are reported in patients with liver disorders (10), such as: a) processes of liver necrosis, inflammation and regeneration, such as acute hepatitis caused by any virus (hepatitis A, B and C or cytomegalovirus); b) acute liver failure of any aetiology (paracetamol overdose, autoimmune hepatitis, Wilson's disease, idiosyncratic drug reactions, ischaemic hepatitis), where 36% of patients exceed 20 μg/L and, in some cases, may even be 180 times above the upper reference limit (11); c) chronic hepatitis of any aetiology, whether viral, autoimmune, toxic, fulminant, cirrhosis of the liver or liver abscesses, where values up to ten times above the discriminant value may be observed (12–14). In children under 3 months of age with atresia of the bile ducts or hepatitis, α-fetoprotein concentrations of between 1000 and 3500 times the upper reference limit may be observed (15). Elevated concentrations of α-fetoprotein have also been reported in patients treated with various drugs that may cause hepatotoxicity: chemotherapy in patients with testicular cancer, or in patients receiving anaesthetics or antiepileptics (16, 17).

Values of up to 140 times the upper reference limit have been described in cases of hereditary tyrosinaemia type I, with 71% of patients showing levels twice the upper reference limit (18). On the other hand, in hereditary persistence of this tumour marker increased concentrations have been observed (19, 20), and in ataxia-telangiectasia values of up to 50 times the discriminant value have been described (21). Considerable increases in the concentration of α-fetoprotein have been reported in a patient suffering peritoneal tuberculosis (22) and in pregnant women with systemic lupus erythematosus (23).

CA 125 antigen

CA 125 antigen is a high molar mass glycoprotein present in structures derived from Müllerian ducts and the mesothelium.

One of the main causes of false positives for CA 125 antigen concentration is fluid effusion and retention. In patients with benign effusion, Trapé et al. (24) found that the concentration of CA 125 antigen may reach up to a 100 times the discriminant value, with the mean being between

Table 1 Main causes of elevation of the concentration of various tumour markers in absence of neoplasia.

	AFP	β-hCG	β_2M	CA 15-3	CA 19-9	CA 125	CA 72-4	CEA	CgA	CYFRA	HER-2	NSE	Pro-GRP	PSA	S-100	SCC	Tg
Pre analytical/iatrogenic	+[a]	ND	ND	ND	ND	+[b]	+++[c]	ND	+[d]	+[c]	ND	ND	ND	+[e]	ND	ND	ND
Hepatobiliary diseases	+++	+	+	+	+++	+	+	+	+	+	+	+	+	ND	++	+	ND
Renal failure	ND	+++	+++	+	+	+	+	+	++	+	+	+	++	+/-[f]	++	++	ND
Pneumonitis/pulmonary fibrosis	ND	ND	ND	+++	++	++	+	++	+	++	ND	+	+	ND	ND	ND	ND
Effusion	ND	ND	ND	ND	ND	+++	ND	ND	ND	+	ND	ND	ND	ND	ND	++	ND
Pneumonia/chronic obstructive pulmonary disease/ tuberculosis	+	ND	ND	ND	++	++	ND	+	+	+	ND	+	+	ND	ND	+	ND
Pancreatitis	ND	ND	ND	ND	+++	ND	+	+	+	ND	ND	ND	ND	ND	ND	ND	ND
Gastrointestinal diseases	ND	ND	ND	+	+++	+	+	+	++	ND	ND	ND	+	ND	ND	ND	ND
Hypothyroidism	ND	ND	ND	ND	ND	+	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hyperthyroidism	ND	ND	ND	+	ND	ND	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND
Vitamin B_{12} deficiency	ND	+[g]	ND	+++	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Endometriosis/ gynaecological diseases	ND	ND	ND	+	+++	++	+	+	+	ND	ND	ND	ND	ND	ND	+	ND
Pregnancy	+++	+++	ND	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	++
Autoimmune diseases	+	++	+	+	+	++	ND	+	+	ND	ND	+	ND	ND	+	+	+++
Haemolysis	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+++	ND	ND	ND	ND	ND
Prostatitis/BPH	ND	ND	ND	ND	ND	ND	ND	ND	++	ND	ND	ND	ND	+++ +	ND	ND	ND
HIV/CMV/viral infection	ND	ND	++	ND	ND	ND	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND
Cardiovascular diseases	ND	ND	ND	ND	ND	+++	ND	ND	+++	ND	ND	ND	ND	ND	ND	ND	ND
Skin diseases	ND	ND	+	+	ND	+	ND	+	ND	ND	ND	ND	ND	ND	+	+++	ND
Cerebral lesions	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	+	ND	ND	++	ND	ND

AFP, α-fetoprotein; β-hCG, choriogonadotropin (β chain); β_2M, β_2-microglobulin; CA 15-3, CA 15-3 antigen; CA 19-9, CA 19-9 antigen; CA 125, CA 125 antigen; CA 72-4, CA 72-4 antigen; CEA, carcinoembryonic antigen; CgA, chromogranin A; CYFRA, CYFRA 21-1 antigen; HER-2, HER-2/neu oncogenic protein; NSE, neuron-specific enolase; Pro-GRP, progastrin releasing peptide; S-100, S-100 protein; SCC, squamous cell carcinoma antigen; Tg, thyroglobulin; ND, not described; +, elevation of the tumour marker concentration up to three times the upper reference limit; ++, elevation of the tumour marker concentration between four and ten times the upper reference limit; +++, elevation of the tumour marker concentration more than ten times the upper reference limit. [a]Chemotherapy and hepatotoxic drugs; [b]abdominal surgery; [c]ibuprofen in patients with pericardial effusion; [d]omeprazole; [e]prostatic message, RTU; [f]reduction of the PSALL/PSA ratio in patients on dialysis with low-flow membranes; [g]only reported for the β-hCG free fraction.

five and six times above this limit. Similar values are described in hepatopathies with ascites (25), whereas only 10% of patients without ascites present values above the upper reference limit, and none of them present scores ten times above this value. Considerable increases have been reported in severe hypothyroidism, especially when associated with effusion (26).

In benign ovarian disease the concentration of CA 125 antigen may increase to two or three times the upper reference limit (27), but in Meigs' syndrome concentrations of CA 125 antigen of up to 50 times the discriminant value have been reported (28).

In congestive heart failure notable elevations in the CA 125 antigen concentration were reported to correlate with the severity of the condition and with the concentration of Brain Natriuretic Peptide (BNP). No false positives were observed in class I or II patients (New York Heart Association classification – NYHA); class III patients present mean values close to twice the upper reference limit whereas class IV patients have values seven times above this limit (29). In this context Nuñez et al. (30). reported that 66% of patients presented values above the cut-off limit and at 6 months presented mortality risks of 2.51, 4.91 and 8.49 in patients in quartiles 2, 3 and 4, respectively. Increases of this biological magnitude have been described during the menstrual cycle in 5% of women studied, even though their values were less than twice the upper reference limit (31). In the menstrual phase of the cycle the reported percentage of false positives is 5.5%, whereas in the follicular and luteinic phases the number of false positives is $<2\%$. However, the authors of that study did not report any increases in the concentration of CA 125 antigen above the upper reference limit during the peri-ovulatory period. The lowest numbers of false positives were in the follicular, peri-ovulatory and luteinic phases. This behaviour is very different from the CA 15-3 antigen concentration, making it difficult to make a firm recommendation regarding the period of the menstrual cycle in which the extraction should be made if the two values are to be measured simultaneously.

Talbot et al. (32) reported increases up to three times the upper normal limit in 62% of patients undergoing abdominal surgery 3 weeks after the intervention.

In patients with renal failure Filella et al. (4) reported that the concentration of CA 125 antigen increased in 17% of patients without haemodialysis and in fewer than 10% of patients receiving this treatment. The authors observed moderate elevations in the CA 125 antigen concentration: up to five times the upper reference limit in the first group of patients and up to twice this limit in the second.

Increases in the concentration of this marker have also been described in lung diseases, including active tuberculosis, with values of up to four times the discriminant value. Mean concentrations of CA 125 antigen in excess of twice the discriminant value have been described in chronic obstructive pulmonary disease, pneumonia, interstitial pulmonary disease and lupus erythematosus (33, 34).

During pregnancy the concentration of this tumour marker increases after the tenth week of gestation and remains high until the end of the pregnancy, when the concentration of CA 125 antigen may be twice the upper reference limit.

Finally, using certain measurement systems, false positives of the CA 125 antigen concentration were reported in relation to the presence of heterophil antibodies (35).

CA 15-3 antigen

In the absence of neoplasia, it is possible to find concentrations of CA 15-3 antigen ten times above the upper reference limit in patients with cobalamin deficiency (vitamin B_{12}) and macrocytosis. The patients with highest concentrations of CA 15-3 presented lower cobalamin concentrations and higher concentrations of L-lactate-dehydrogenase (LDH) (5). In patients with different inflammatory myopathies, 22% present CA 15-3 antigen values above the reference limit (36). Collazos et al. (37) describe increases in the CA 15-3 antigen concentration in 11% of patients with cirrhosis and in 6% of patients with liver disease without cirrhosis. In another study, these same authors (38) observe that patients with an immunoglobulin A concentration above the upper reference limit present an increased CA 15-3 antigen concentration. Elevations of up to ten times the upper reference limit have been reported in interstitial pulmonary disease, and increases of twice this limit in pneumonitis associated with collagen diseases (39). Treatment with granulocyte colony stimulating factor (G-CSF) increases the concentration of CA 15-3 antigen to up to twice the upper reference limit during treatment, with the level dropping to the reference interval once treatment is discontinued (40).

In systemic sclerosis 14% of false positives are found to be related to high concentrations of C-reactive protein and antinuclear antibodies, and with involvement of the knee (41). Increases in the concentration of CA 15-3 antigen are also reported in diseases with ovarian cysts (42). In polymyositis, values of up to five times the upper reference limit have been recorded for this antigen (39).

Increases of this value to twice the upper reference limit were also described during the menstrual cycle in 7% of patients (31). The proportions of women with a CA 15-3 antigen concentration above this limit at different phases of the menstrual cycle were 3%, 7%, 6% and 6% in the menstrual, follicular, peri-ovulatory and luteinic phases, respectively. The authors found no significant differences between the concentrations of the different phases of the menstrual cycle. It is therefore recommended that any measurement of the CA 15-3 antigen concentration be made during the menstrual phase, so as to reduce the number of false positives. In renal failure there is a discrepancy in the references consulted: while some authors report that 4.5% of patients may exceed the upper reference limit by up to five times (4), others find no differences compared to healthy individuals (43). Molina et al. (44) reported increased values of up to double the upper reference limit in benign gastrointestinal disease including ulcerative colitis, Crohn's disease, pancreatitis, hepatitis, cirrhosis of the liver and cholecystitis.

CA 19-9 antigen

CA 19-9 antigen is a mucinous antigen with a high molar mass. The epitope that recognizes this antigen is a glycolipid silalactone-N-fucopentaose II ganglioside, which is the sialized derivative of the Lewis A blood antigen. Patients with a Lewis a-b- phenotype do not express this antigen and represent 5% of the population. In the absence of cancer, increased concentrations of CA 19-9 antigen have been observed in 1%–4% of subjects (45) and also in different benign diseases.

Hepatobiliary diseases are a frequent cause of false positives, particularly when the patient presents jaundice (46, 47). Between 20% and 25% of patients with cirrhosis of the liver have concentrations above the upper reference limit (48, 49). In patients with chronic hepatitis this figure is only 10%; it is 54% in obstructive jaundice of extra-hepatic origin (50). In 34% of cases, the increased concentration of this tumour marker is more than double the upper reference limit and in 11.5% of cases its value exceeds this limit by ten times. In acute cholecystitis the number of false positives is as high as 71% (49).

So the concentrations of CA 19-9 antigen reported in hepatobiliary diseases may be extremely high. Murohisha et al. (3) reported values 1000 times the upper reference limit in a patient with a calculus in the bile duct complicated with cholangitis, as did Akdoğan et al. (51) in a patient with cholangitis and a pancreatic pseudocyst. Finally, after evaluating a series of patients with benign diseases of the biliary tract, Albert et al. (52) indicate that cholangitis is the cause of marked increases in the antigen CA 19-9 concentration. All these data highlight the role of the liver and the bile duct in the metabolization and elimination of CA 19-9 antigen.

Elevation of the CA 19-9 antigen concentration above the upper reference limit may also be observed in patients with acute and chronic pancreatitis, both due to inflammation of the pancreas and to the possible implication of the bile ducts in the process. Klapdor et al. (49) observed increases of this value in 88% of acute cases of pancreatitis and in 5% of chronic cases of pancreatitis. Piantino et al. (53) indicate that the antigen CA 19-9 concentration is elevated in 40% of patients with acute pancreatitis. Furthermore, Petit et al. (54) observed increased concentrations of this tumour marker in patients with decompensated diabetes mellitus.

Buccheri et al. (55) found an increased concentration of CA 19-9 antigen in 18 of 57 patients with benign pulmonary disease, whereas Vendimian et al. (56) reported an increase in four of 25 patients with this disease. Takayama et al. (57) highlighted the percentage of false positives in the CA 19-9 antigen concentration in patients with benign pulmonary disease, particularly tuberculosis (52%), bronchiectasis (59%) and idiopathic pulmonary fibrosis (81%). Elevated concentrations of CA 19-9 antigen were also observed in patients with cysts and pseudocysts in different locations (58–60). The percentage of false positives in other pathologies was considerably lower than that described above. Filella et al. (4) observed an increase of 6% for this value in patients with kidney failure treated with haemodialysis and Sakamoto et al. (48) reported increased values in 9% of a group of patients with peptic ulcer. Finally, increased concentration of this tumour marker was described in endometriosis (61), in rheumatic diseases (62) and in relation to excessive consumption of tea (63).

In a recent study, Stieber et al. (64) described CA 19-9 antigen concentrations of more than ten times the discriminant value in patients with benign gastrointestinal diseases including cirrhosis, Crohn's disease, gastritis and cholecystitis. A small increase of 1.5 times above upper reference limit was found in one patient with hypothyroidism, who returned to normal limits after treatment with thyroxin (65).

CA 72-4 antigen

CA 72-4 antigen is a high molar weight mucin identified by monoclonal antibodies B72.3 and cc49 of the glycoprotein associated with tumours 72. Filella et al. (66, 67) reported that 5% of pregnant women present CA 72-4 antigen concentrations of more than double the upper reference limit. They also reported values above this limit in 5% of patients with benign gastrointestinal or heart disease, 4% in hepatopathies, 6% in pulmonary disease (especially pneumonia, 9%), 10% in benign gynaecological diseases (especially ovarian cyst, 25%) and found that the majority of patients with values above the upper reference limit suffered from rheumatoid disease.

Halm et al. (68) reported that between 3% and 7% of patients with pancreatitis presented values above the upper reference limit. Balaban et al. (69) found concentrations of CA 72-4 antigen above the upper reference limit in 50% of patients with familial Mediterranean fever. They also mentioned the existence of significant differences between the concentrations in this group of patients and healthy individuals.

In patients with pericardial effusion treated with ibuprofen there were elevations of more than ten times the upper reference limit, which fell on discontinuation of treatment (70).

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA) is a high molar mass glycoprotein belonging to the immunoglobulin family.

This antigen is expressed in different tissues, including the stomach, large intestine, pancreas and lungs. Inflammatory processes or necrosis of these organs release considerable amounts of CEA and increase the concentration above the upper reference limit. Elevation of the concentration of this tumour marker has been reported in pancreatitis (71), diverticulitis, peptic ulcer and diseases where the CEA concentration can reach figures four or five times above the discriminant value. In inflammatory intestinal disease it has been reported that the number of false positives increases with the severity of the disease reaching maximum values between four and eight times above the upper reference limit in cases of serious disease (72). There have also been reports

of increases in the CEA concentration of up to two and three times the upper reference limit in pneumonia caused by different micro-organisms, including bacteria (73), fungi (74, 75) and tuberculosis (76). High values of this marker have also been observed in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis (77).

CEA concentration is increased in diseases that affect organs involved in its metabolization (liver) and elimination (kidneys). Filella et al. (4) reported increases of this value in patients with renal failure and found a correlation between the concentrations of creatinine and CEA. There were more false positives in patients treated with haemodialysis than in those not treated (47% compared to 30%) and higher CEA concentrations in treated patients (five times the reference value, compared with three times). Another organ involved in the metabolism of CEA is the liver. George et al. (78) described CEA values of up to four times above the discriminant value in patients with fulminant hepatitis (with mean values of 1.5 times this figure). In obstructive jaundice the mean values were up to double the upper reference limit. Patients with benign tumours, sclerosing cholangitis and choledochal cysts presented higher values of around 20 μg/L (79), with maximum values in patients with choledochal cysts. Collazos et al. (80) found increases in the concentration of this tumour marker in 38% of patients with cirrhosis, with increases in 42% of patients in Child Pugh stages B and C and in only 28% of those in stage A.

Increased CEA concentrations have been reported in 7% of patients with adnexal masses (81). Amino et al. (82) described elevations in the concentration of this tumour marker in patients with hypothyroidism which correlated directly with the duration of the hypothyroidism and inversely with the concentration of thyroxine. Finally, false positives have been observed in the CEA concentration, sometimes with notably high values, which cannot be attributed to any cause. Shapiro et al. (83) reported one case in which this value was 44.9 μg/L, but the authors were unable to discover the cause of the increase.

CYFRA 21-1 antigen

CYFRA 21-1 antigen is composed of soluble fragments of cytokeratin 19 identified by BM 12.21 and KS19.1 antibodies.

In benign pulmonary diseases the largest elevations are observed in processes of interstitial pulmonary fibrosis, with increases above the upper reference limit in 50% of cases (reaching values of 11.0 μg/L). In pulmonary fibrosis associated with collagen diseases, 30% of patients are above the upper reference limit (with values as high as 20.0 μg/L). This marker may also present increases in patients with tuberculosis or chronic obstructive pulmonary disease of up to two and three times the upper reference limit, and may even reach values three times above the discriminant value (84).

Among patients with lung disease, CYFRA 21-1 antigen concentrations were found to be above the upper reference limit in patients with radiation-induced pneumonitis (85). In patients with renal failure (86) treated with dialysis there are more false positives in cases of peritoneal dialysis, with 73% of patients above the upper reference limit, compared with 57% of patients on haemodialysis (87). Finally, elevations of the CYFRA 21-1 antigen concentration were observed in patients with diabetic nephropathy (88), in patients with benign pleural effusion and renal failure (89) and in patients with cirrhosis of the liver (with concentrations between two and three times above the discriminant value) (90). A recent study reported increases of up to twice the upper reference limit in patients with pericardial effusion treated with ibuprofen (700).

Squamous cell carcinoma antigen

Squamous cell carcinoma antigen (SCC) is an epithelial glycoprotein belonging to the family of serinprotease inhibitors. Two isoforms are known, SCC-1 and the SCC-2. These molecules are synthesized in squamous tissues of the cervix, vagina, vulva, oesophagus, skin and lungs and so it is not surprising that elevations of their concentration are related to diseases of these tissues. In obstructive pulmonary disease the percentage of false positives ranges between 15% and 40% with maximum values close to ten times the upper reference limit (91–93). Increases above the upper reference limit in the concentration of this tumour marker were also reported in 65% of patients with tuberculosis (94), whereas concentrations between four and five times this limit were found in patients with pleural effusion of non-neoplastic aetiology (95). Upham et al. (96) found no elevations in patients with this type of disease. In the sleep apnoea syndrome increases were reported in 4% of patients (91).

In dermatological diseases, concentrations of this tumour marker above the upper reference limit have been described in patients with psoriasis, eczema, pemphigus, epidermitis, erythrodermia, psoriasis and atopic dermatitis. Furthermore, in the majority of these diseases there is a correlation between the values of the SCC antigen concentration and the skin surface area affected. The maximum values reported are ten times the discriminant value (97–100).

The SCC antigen is eliminated through the kidney, and so its concentration is increased in patients with kidney disease. Concentrations of SCC antigen above the discriminant value have been described in 43%–47% of patients with chronic renal failure without haemodialysis (with mean concentrations close to twice the upper reference limit) with maximum values between seven and ten times above the cut-off, while in haemodialysis patients this percentage increases to 72%–77% (4, 91, 92). The proportion of false positives varies depending on the type of membrane used for haemodialysis between 98% (cellulose) and 76% (synthetic), with the concentration increasing slightly after dialysis with a cellulose membrane and dropping with a synthetic one (101). Increases in the SCC antigen concentration have been reported when the glomerular filtration rate is below 40 mL/min (102).

Concentrations of SCC antigen above the upper reference limit have been reported in 5%–20% of patients with benign uterine disease (103–106). However, the studies of benign adnexal disease are controversial. Some authors describe elevations in the concentration in 11%–20% of patients, whereas others claim that the values for these patients are physiological (106, 107).

Various authors (108–110) report SCC antigen concentrations above the upper reference limit in 10%–15% of patients with cirrhosis, chronic hepatitis, alcoholic hepatitis and steatosis, sometimes three times above the cut-off. Molina et al. (91) found that 5% of cirrhotic patients present SCC antigen concentrations above the upper reference limit but all of them had kidney dysfunction. Biasiolo et al. (111) describe SCC-1 antigen concentrations above the upper reference limit in 33% of patients with chronic hepatitis.

Prostate specific antigen

Prostate specific antigen (PSA) is an enzyme belonging to the group of glandular kallikreins, mainly synthesized in the prostate gland and secreted in the semen, where its function is to make the semen more fluid. This function gives rise to the name of semenogelase recommended by the International Union of Biochemistry and Molecular Biology and the International Union of Pure and Applied Chemistry (IUPAC) (EC 3.4.21.77). In the absence of cancer, acute prostatitis and benign prostatic hyperplasia are the main causes of increased PSA concentrations. Considerably increased values may be observed in acute prostatitis (112, 113), and so it is necessary to wait for the process to resolve before repeating the measurement of this value.

PSA concentration is above 4 μg/L in 25%–50% of patients with benign prostatic hyperplasia (BPH) (114, 115), and is particularly high in patients with acute urine retention or urinary infection. The concentration of the different PSA fractions, whether non-protein-bonded PSA (free PSA) or PSA bonded to α_1-antichymotrypsin (complexed PSA), are also elevated in BPH. The elevation of the concentration of PSA fractions in this disease is parallel to that of PSA, so the use of the free PSA/total PSA ratio or the complexed PSA/total PSA ratio allows more precise diagnosis of the value/.

PSA concentration is increased by stimulation of the prostate gland, including prostate massage, prostate biopsy, transurethral resection and cystoscopy (116, 117). In most cases there are no significant alterations in the PSA concentration in relation to digital rectal examination, although is a good idea to allow a few days to pass between this examination and measurement of the PSA concentration (118).

Neither is the influence of haemodialysis on PSA and free PSA concentration very clear. Douville et al. (119) indicated that haemodialysis does not affect the PSA concentration, but increases free PSA. On the other hand, Horinaga et al. (120) found that haemodialysis reduces the PSA concentration, whereas Tzanakis et al. (121) found that haemodialysis with low-flow membranes does not eliminate PSA and that as a result haemodialysis would increase the concentration. The differences between the various types of membranes used in haemodialysis were also assessed by Djavan et al. (122). They concluded that while the PSA concentration can be used for screening for prostate cancer in patients on haemodialysis irrespective of the type of membrane used, the free PSA/PSA ratio can only be used if haemodialysis is performed with low-flow membranes.

Measurement systems with a high detection capacity allow measurement of very low concentrations of PSA. These systems have identified PSA concentrations in the plasma of women, indicating that PSA is produced in sites other than the prostate gland. In an initial series of three articles in 1994, Yu and Diamandis et al. (123–125) reported the presence of PSA in tissue in breast cancer. These authors later detected the presence of concentrations of this tumour marker in the milk of breast-feeding women, in amniotic fluid, and in the plasma of healthy women and women with breast cancer (126–128).

Later, other groups described the presence of PSA in non-prostate tissues. Filella et al. (129, 130) observed the presence of PSA in amniotic fluid and milk of breast-feeding women, as well as in the breast secretion of non-breast-feeding women, in breast cysts, and in bronchoalveolar lavage of patients suffering pneumonia. Apart from breast cancer, PSA has been observed at tissue level in various tumours ranging from colon cancer to kidney tumours (131–133).

Furthermore, concentrations of PSA and free PSA have been detected in the plasma of women with acute pancreatitis and especially in women with pancreatic cancer (134), whereas there are no conclusive data about whether hepatopathies may increase PSA concentration. Bosch et al. (135) described increases in the concentration of this tumour marker in acute type A hepatitis, but Malavaud et al. (136) and Kilic et al. (137) found that hepatopathies do not affect the values of this marker.

β_2-Microglobulin

β_2-Microglobulin is a high molar mass protein mainly eliminated by the kidney. Processes involving kidney failure lead to a considerable increase in the concentration of β_2-microglobulin. In patients with renal failure and treated with haemodialysis, mean values of 20 times the upper reference limit have been reported, and occasionally, 30 times higher (138). Increased levels have been described in workers exposed to cadmium and were related to the degree of kidney failure (139).

An increase in the concentration of this marker may also occur in processes of lymphocyte activation, such as viral infections. Increases in the concentration of β_2-microglobulin have been described in infections caused by the AIDS virus (140) and by cytomegalovirus (141, 142). Some publications describe a parallel evolution of β_2-microglobulin concentration with the control of treatment for infections caused by the hepatitis B virus (143, 144). Collazos et al. (145) proposed using β_2-microglobulin concentration to assess the

treatment of tuberculosis, a disease that also produces increases in this marker. Scangolari et al. (146) reported that the concentration of this tumour marker was twice its normal value, in patients with hepatitis C or multiple sclerosis treated with interferon-γ.

Choriogonadotropin (β chain)

Choriogonadotropin (hCG) is a hormone that comprises two subunits, α and β. The first subunit is also present in other hypophyseal hormones, whereas the β subunit provides its functional specificity. β-hCG is synthesized in large amounts by placental trophoblastic tissue and in much smaller amounts by the hypophysis and other organs, such as the testicles, liver and colon (147).

In the first place, it is necessary to determine which magnitude is measured by the system used in the laboratory, because there may be different molecular forms of β-hCG in plasma. For example, the molecule can be found complete or intact, occult, or hyper-glycated; other forms are the subunit not bonded to protein (free), the fragment core β, the C terminal peptide and the subunit β without the C terminal peptide. Depending on the type of measuring system used, the results obtained may vary considerably (148). When detecting a tumour it is better to use a system capable of measuring the concentration of all possible fragments so as to avoid false low values. When the result is above the discriminant value and not related to pregnancy, the possibility of it being a false positive caused by the presence of heterophil antibodies should be ruled out (149, 150).

Among the most frequent causes of increased β-hCG concentration is chronic renal failure (151): increases of ten times the upper reference limit have been reported in patients undergoing dialysis (152).

Persistently high concentrations of β-hCG have been reported that do not correspond to any specific benign disease, without their being false positives caused by heterophil antibodies or other causes related to the analytical specificity of the measuring system. Palmieri et al. (153) reported the result of follow-up of 14 patients, in three of whom choriocarcinoma was detected; in one patient the concentrations dropped to physiological values following a hysterectomy, and in the remainder increased concentrations persisted for many years without any evidence of tumour.

Significantly high concentrations of free β-hCG have been found in pregnant vegetarians (1.2 times the mean value), and were negatively associated with the cobalamin concentration (vitamin B_{12}) in maternal plasma (154).

Hoermann et al. (147) mention other causes for elevations that do not correspond to pregnancy, tumours, or false positives due to heterophil antibodies, such as menopause or premature ovarian insufficiency.

Increased concentrations of β-hCG were found in 24% of patients with systemic lupus erythematosus, associated with the presence of ovarian or endometrial antigen antibodies (155). Finally, the consumption of marihuana has also been reported to raise the β-hCG concentration (156).

Chromogranin A

This molecule is secreted by the adrenal cells, hypophysis, pancreas, stomach, intestine, lungs, heart and prostate (157). As a result the main elevations of the chromogranin A concentration in the absence of cancer are observed in diseases related to these organs.

Concentrations of chromogranin A above the upper reference limit have been described in patients with benign prostatic hyperplasia (158–160).

Spadaro et al. (161) and Massironi et al. (162) report chromogranin A concentrations ten times above the upper reference limit in patients with chronic hepatitis and cirrhosis of the liver.

Chromogranin A concentrations five times above the upper reference limit are reported in almost all patients with heart disease (161, 163, 164). Increased concentrations of this tumour marker are also observed in patients with acute coronary syndrome (165, 166).

In diseases affecting the respiratory tract, Sobol et al. (167) reported chromogranin A concentrations above the upper reference limit in patients with chronic obstructive pulmonary disease. Sørhaug et al. (168) found concentrations above this limit in smokers with obstruction of the airways.

Ziegler et al. (169) and Kurnatowska et al. (170) reported that patients with chronic renal failure present chromogranin A concentrations above physiological values, and that these values increase in patients undergoing haemodialysis. Furthermore, Spadaro et al. (161) found elevations in 92% of patients, with values up to 30 times the upper reference limit.

Tsao et al. (171) indicated increases in chromogranin A concentration above the upper reference limit in patients with endometriosis and leiomyoma.

Al-Shoumer et al. (172) reported chromogranin A concentrations above the upper reference limit in patients with hyperthyroidism. Furthermore, they concluded that, on the one hand, patients not treated with antithyroid drugs present higher chromogranin A concentrations and on the other that there are significant differences between the values of the marker before and after the drug treatment.

Peracchi et al. (173) reported that 62% of patients with autoimmune atrophic gastritis present chromogranin A concentrations above the upper reference limit.

Increases in this marker above the upper reference limit were also found in inflammatory bowel disease, specifically in ulcerative colitis and Crohn's disease (174).

Some publications (175, 176) report that the administration of low doses of omeprazole over a short period raises the chromogranin A concentration in men with an endocrine or metabolic dysfunction. Sanduleanu et al. (177) reported increases up to twice the upper limit reference in patients during medium- and long-term omeprazole therapy.

γ,γ-Phosphopyruvate-hydratase (''neuron-specific enolase'')

Neuron-specific enolase (NSE) is a glycolytic enzyme that catalyses the reaction of 2-phospho-D-glycerate to phospho-

enol pyruvate. There are five known isoenzymes of enolase comprising the combination of three subunits α, β and γ. The isoenzyme with two γ subunits is mainly synthesized in the central and peripheral neurons and in neuroendocrine cells.

The most common cause of false positives for NSE is haemolysis of the sample due to a high content of the enzyme in erythrocytes (178). Medical conditions that increase the NSE concentration are related to renal failure, a complaint in which 36% of false positives are observed with concentrations two or three times above the upper reference limit (4). Muley et al. (179) reported a NSE concentration of three times above the upper reference limit in patients with benign pulmonary disease. Moreover, increased NSE concentrations have been reported in 27% of patients with tuberculosis (180).

The brain is one of the organs with a high NSE content, since this enzyme is present in the central and peripheral neurons. Vos et al. (181) found mean NSE concentrations in head injury patients of twice the upper reference limit; values of this marker above 21.5 μg/L were considered a sign of poor prognosis. In addition, NSE concentrations of up to ten times the upper reference limit were observed in stroke patients (182). In patients with severe insulin-induced hypoglycaemia, one case presented a NSE concentration five times the upper reference limit (183).

Collazos et al. (184) reported that 5% of patients with hepatopathies present values for this marker of up to twice the discriminant value. Massabki et al. (185) found that one third of patients with systemic sclerosis present a NSE concentration above the upper reference limit, reaching maximum values of five times above the cut-off point.

HER-2/neu oncogenic protein

HER-2/neu oncogenic protein is the soluble fraction of the HER-2 membrane receptor, a molecule that is over-expressed in some breast carcinomas.

Sugano et al. (186) noted the existence of false positives in patients with benign hepatopathies, including hepatitis and cirrhosis of the liver. Equally, Molina et al. (187) reported that the concentration of this tumour marker increases in various non-cancerous diseases including benign conditions of the breast, peptic ulcer, renal failure and lupus. On the other hand, these authors indicate that in patients with cirrhosis of the liver the proportion of false positives is 38.5% and suggest that this protein is catabolised in the liver. In addition, Motoo et al. (188) reported an increase in the concentration of this tumour marker in 63% of cases of cirrhosis of the liver, in 43% of cases of acute and chronic hepatitis and in 30% of cases of cholelithiasis.

Progastrin releasing peptide

Progastrin-releasing peptide (Pro-GRP) is a peptide of 27 amino acids, a homolog of the bombesin isolated in pig stomach.

Renal failure is the most frequent cause of false positives in the case of Pro-GRP, with reports of values of up to 145 μg/L (189). In one study, 93% of patients on haemodialysis presented a Pro-GRP concentration above the upper reference limit (87). Molina et al. (189) described Pro-GRP concentrations close to 90 μg/L in non-infectious pulmonary diseases and up to 96 μg/L in diseases of the digestive tract. Lower values, but also above the upper reference limit, have been described in patients with acute hepatitis. In any case, the largest increases reported for this biological marker are not more than three times the upper reference limit.

Protein S-100

Protein S-100 is a low molar mass dimeric protein belonging to the family of calcium-binding proteins. It is mainly synthesized by astroglial cells and melanocytes.

The main routes of elimination of protein S-100 are via the liver and kidneys. As a result, diseases affecting these organs are the basic causes of false positives. Elevations in the protein S-100 concentration have been reported in 46% of patients with renal failure, in some cases even reaching values 20 times above the upper reference limit. It has been observed that 63% of patients with cirrhosis of the liver present protein S-100 concentrations above the discriminant value, even though the majority of patients presented values not more than 2.5 times this limit and the highest value do not exceed it by more than 3.5 times (190).

Udén et al. (191) describe moderate increases in patients with infectious diseases, both with or without cerebral involvement, although the highest values and largest percentage of false positives occur in patients with cerebral involvement. Increases in the protein S-100 concentration have also been described in patients with cerebral lesions with necrosis due to traumatic processes (192) or ischaemic or haemorrhagic stroke (193).

Finally, elevations in the protein S-100 concentration of between two and three times the upper reference limit were found in patients with systemic lupus erythematosus and neuropsychiatric involvement (194).

Thyroglobulin

This high molar mass protein is rich in tyrosines synthesized by the thyroid follicular cells. Thyroglobulin concentrations are extremely high in cord blood and plasma of babies, and fall progressively with age (195).

Increases in the thyroglobulin concentration above the upper reference limit are observed in the third trimester of pregnancy and in various medical conditions, such as Graves' disease, sub-acute thyroiditis, toxic adenoma, and infiltrations of the thyroid by other malignant tumours (196–198).

Correct interpretation of the values obtained for this marker must consider that the presence of circulating anti-thyroglobulin autoantibodies could interfere with the measurement of the thyroglobulin concentration in some measuring sys-

tems (depending on whether the measurement principle is competitive (199) or non-competitive immunoanalysis) (200, 201). Therefore, the anti-thyroglobulin autoantibody concentration should be measured in conjunction with the thyroglobulin concentration during follow-up of patients with thyroid cancer (202).

Conclusions

Identifying the causes of an elevation in a tumour marker concentration in the absence of cancer (false positive) is vital to the correct interpretation of tumour marker results. The objective of this revision was to examine the different circumstances that could give rise to these false positives. The main limitation is the disparity of results published, most probably because of deficiencies in the standardization of the systems used to measure the concentration of different tumour markers. This diversity in the concentrations obtained with different assay methods is primarily reflected by the differences in the upper reference limits proposed in relation to the particular method used, and in the selection of the reference population used to define the discriminant value for each marker studied. In spite of this, we observed a certain coincidence in the conclusions reported in the successive studies (a total of 204) reviewed here.

As already mentioned, there are many possible causes for high tumour marker concentrations in the absence of cancer. Sometimes the increase is so large that it prevents us from distinguishing between benign disease and advanced cancer; for instance, the CA 19-9 antigen presents similar concentrations in patients with jaundice and in patients with pancreatic cancer. Table 1 shows the main causes for elevation of tumour marker concentrations in the absence of cancer; the plus signs indicate the degree of the increase.

The false positives for tumour markers are related to the patient's condition as well as to pre-analytical or iatrogenic factors, interference due to the assay method used and, finally, various non-cancerous diseases. In some cases there are clinical tests that can identify these false positives. For example, a series of biological measurements can be performed in the laboratory to provide information about whether the patient could have one of these diseases: for instance, creatinine concentration can be measured in order to detect kidney dysfunction. Pleural effusion, which is related to CA 125 antigen elevation in the absence of cancer, can be diagnosed by chest X-ray. Moreover, some characteristics of the systems used to make the tumour marker measurements must be taken into consideration, because this may help to identify some of the causes of false positives and thus allow appropriate action to be taken. Finally, knowledge of the different diseases that affect each individual may aid interpretation of the concentration of a tumour marker in the specific context of each patient.

The principles displayed in Table 2 form the basis of the following recommendations designed to improve interpretation of the results of tumour marker concentrations and to prevent diagnostic errors derived from false positives.

These recommendations may help to improve the interpretation of the results of tumour marker concentrations in the particular context of each patient, and can contribute to the diagnosis, prognosis and follow-up of cancer patients.

Table 2 Recommendations for improving the interpretation of tumour markers and preventing diagnostic errors derived from false positives.

Thorough awareness of the patient's condition.
1. For example, certain manipulations of the prostate may raise PSA, and treatment with ibuprofen is related with increased CA 72-4.
Pre-analytical factors.
1. Some tumour markers are particularly labile (for instance, free PSA) and others, like neuron-specific enolase, are increased in the event of haemolysis of the sample.
Establishing the specificity of the measuring equipment used.
For example, it is vital to know of the possible existence of crossed reactivity with other molecules similar to those being assayed: for example, neuron-specific enolase with other enolase isoenzymes.
Detecting interference from heterophil antibodies. The following strategy is recommended:
I. Repeat the assay using another method that should preferably use antibodies from another animal.
II. Perform a heterophil antibody-blocking test (203, 204).
III. Make different dilutions of the serum and check that the results for the dilutions are proportional.
IV. Make a reading of the concentration of the tumour marker in urine, if the molecule is eliminated by this route (for example, β-hCG), and compare the result with that of plasma.
Identifying false positives caused by deficient elimination metabolization of tumour markers by using other biological indicators of kidney and liver function
Identifying, using various biological variables, any benign diseases that might raise the concentration of a tumour marker in the absence of cancer.
For example, a cobalamin deficit might raise the CA 15-3 antigen concentration.
Identifying false positives by observing the evolution of the tumour marker concentration over a period of 3–4 weeks between two consecutive readings. If there is no increase, or if it is below the biological variability established for each marker by the guidelines issued by scientific organisations (205), the elevation could be attributed to a false positive.
Design requests where clinicians report diseases that could increase tumour marker concentrations in the absence of cancer

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