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How CA 125 is used in routine clinical practice

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Abstract

The only role where the CA 125 test has proven utility is: (i) for monitoring ovarian cancer (OC); and (ii) for a preoperative test in patients with an ovarian mass. The aim of our study was to assess the clinical indications for CA 125 determinations in order to estimate the appropriateness of CA 125 use. During the period of 1 August 1993 through 31 December 1995 all CA 125 assays performed at the laboratory of the Institut Central des Hôpitaux Valaisans (ICHV) and the data of the patients receiving these tests were audited in order to identify the clinical indication for the test. We have considered as 'correct indication' a CA 125 test performed: (i) during follow-up monitoring of patients having an OC and; (ii) as a preoperative test of a suspect ovarian mass. 462 patients have received a total of 1057 CA 125 assays. 84 (18%) patients have received 537 (51%) tests for monitoring OC and 68 (15%) patients, 68 tests (6%) as a preoperative evaluation for an ovarian mass. 310/462 (67%) other patients have received 452/1057 (43%) CA 125 tests for screening purposes in various clinical situations. Therefore, only 33% (152/462) patients including 57% (605/1057) of tests, had CA 125 assessments done for the correct indication. The current pattern of practice shows that a great number of CA 125 requests were inappropriate. Educational actions aimed at laboratory users concerning the optimal use of CA 125 should be considered in order to develop a more rational approach.

Keywords: CA 125; Cancer; Ovary; Screening; Tumour markers

1. Introduction

Originally the majority of clinical studies on tumour markers evaluated their possible use as screening, diagnostic, staging or prognostic tools. However, for the CA 125 test as for most other tumour markers, the sensitivity was insufficient for screening of early stage cancer [1–3]. Women with an increased serum CA 125 value may have multiple diagnoses other than epithelial ovarian cancer. Other malignancies such as endometrial, fallopian tube, cervical, breast, colorectal, pancreatic, stomach, biliary tract, liver and lung cancer; or non-malignant conditions such pelvic inflammatory disease, endometriosis, ovarian cysts, cirrhosis, hepatitis or physiological conditions such as menstruation or first trimester pregnancy have all been shown to be associated with elevated CA 125 levels [4–9]. An increased value has furthermore been reported in approximately 1–5% of healthy women [5–10,11].

Published data have demonstrated that serum CA 125 is of clinical usefulness in the preoperative diagnosis of a suspect ovarian mass and in the monitoring of ovarian malignancy [10–13]. Currently screening for ovarian cancer with CA 125 is not recommended because of lack of scientific evidence that deaths from ovarian cancer are decreased by screening and because of potential adverse effects of screening [1,10,12–15]. However, despite these well known limitations, CA 125 has received widespread media attention as a potential screening tool. This may, together with the increasing information on the Internet, incite women to ask to be tested. In consequence ovarian cancer (OC) screening finds a real market. Every year, millions of CA 125 tests are performed. The manufacturer of CA 125 (Centocor, Inc.) reports that in 1993, 4 million tests were performed. Few data are available on the amount of testing which can be attributed for monitoring OC patients or for screening. The aim of our study was to assess how CA 125 testing is used in routine clinical practice.

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2. Patients and methods

The Institut Central des Hôpitaux Valaisans (ICHV) is a regional institution including an analytical laboratory covering chemistry, haematology, infectiology, serology and immunology as well as a Pathology Institute and the Valais Cancer Registry. The ICHV covers a well-defined region, both geographically and politically with a total population in 1995 of 272 000, a population of women 20–80 years of age of 100 000 and 50–70 years of age of 27 000 [16]. The region has seven acute care hospitals and several geriatric hospitals. All of them addressed their tumour markers' analysis and cytological or histopathological exams to the ICHV. Because of referral patterns, it was considered unlikely that persons who lived and have been hospitalised in the study region would have a CA 125 assay or a pathological examination performed outside the ICHV. However, patients followed by doctors in private practice may have some CA 125 assays performed in private laboratories and these data were not collected in the present study.

All data of patients having a CA 125 assay determined at the ICHV were reviewed. Patients with OC have been identified with the data of the Cancer Registry and patients having a cytological or histological exam. in the 3 months before or after the CA 125 assay were abstracted from the data of the Institute of Pathology. All these data were reviewed in order to identify information about the clinical problem for which a CA 125 test has been performed.

For this study we have considered the following situations as a valid indication for a CA 125 request: (1) a preoperative test for a suspicious ovarian mass as a prediction of the benign or malignant nature of an ovarian mass and as verification of OC125 (CA 125) antigen expression; (2) tests in the follow-up of patients having chemotherapy for an epithelial OC and in the follow-up of patients with an epithelial OC after a primary treatment of epithelial OC. A value greater than 35 U/ml was considered a positive CA 125 test result. In the period and in the region under study, no clinical trials involving CA 125 have been performed.

3. Results

3.1. CA 125 assays and patients characteristics

A total of 1057 CA 125 assays have been performed between 1 August 1993 and 31 December 1995. These tests form the basis of the present study. In 1993, 183 assays have been realised, in 1994, 469 and in 1995, 405. Over this 29-month period, a mean of 36 assays (range: 19–59) per month were performed. Among the 1057 samples, a total of 458 (43%) had a value greater than 35 U/ml.

A total of 462 patients (444 women and 18 men) have received at least one CA 125 assay in the period under study and form the population basis of the present study (Fig. 1). The group ranged in age from 18 to 94 years, with a mean age of 58.8 years and a median age of 60 years. Approximately half of the female patients tested (203/444 (46%)) were aged between 50 and 70 years old and 560 (53%) of the total number of tests were performed for this group of patients. As the whole female population of the region with an age of 50–70 years was 27 000 in 1995, this corresponds to 0.8% of all women who have received at least one CA 125 test over the 29-month period.

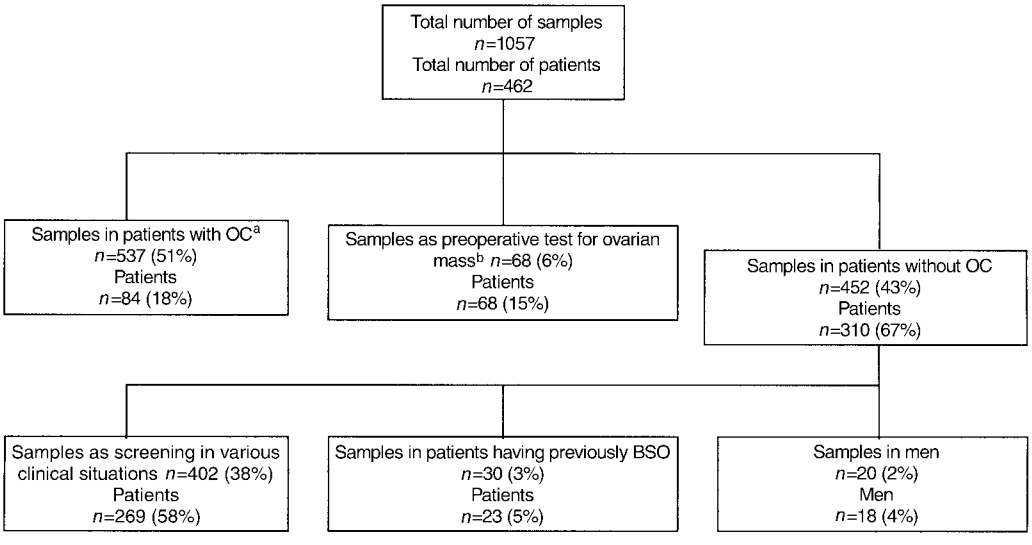

Fig. 1. Distribution of patients and CA 125 samples. OC, ovarian cancer; BSO, bilateral salpingo-oophorectomy. [a]The patients investigated for an ovarian mass who had an ovarian cancer are included in this box. [b]None of these 68 patients investigated for an ovarian mass had an ovarian cancer.

3.2. Patients with an OC or a past history of OC

Among the 444 women, 84 (18%) had CA 125 test(s) for monitoring OC. For 32 patients the diagnosis was known before 1 August 1993 and for 52 patients the diagnosis of OC was established in the period under study. A total of 537 (51%) assays have been performed for these patients. In patients having chemotherapy, a monthly follow-up was realised in practically all patients. In the follow-up after primary treatment there was a considerable variance with which CA 125 monitoring was performed. This varies from only one assay to as many as 30 assays over the 29-month period. Among the 84 patients with OC, 79 presented an epithelial ovarian cancer. 5 patients had a tumour of a histology other than epithelial and have received a total of 11 assays.

3.3. Patients without history of ovarian cancer

In women without a history of OC ($n=378$) 520 (49%) assays have been performed. The median value of these results was 21 U/ml and ranged from 0 to 2808 U/ml. Among false-positive tests (patients without OC and CA 125 assessments >35 U/ml), 129 (25%) were >35 (U/ml); 84 (16%) >65 (U/ml); 64 (12%) >100 (U/ml) and 6 (1%) >1000 (U/ml). For the 6 patients having a CA 125 value exceeding 1000 U/ml, the diagnosis was in 4 cases a metastatic breast cancer, in 1 case advanced cervical carcinoma and in 1 case a liver cirrhosis of unknown origin. For 68 patients the indication was to investigate an ovarian mass, for 74 patients to investigate breast disease (newly diagnosed breast cancer, breast cancer relapse, mastitis or breast abscess), for 46 patients to help search for the origin of a cancer. Other indications have been summarised in Table 1. For 177 (39%) tests, no information about the indication was available, but none of these tests concerns patients with an ovarian cancer.

Among the 462 patients, 18 were men (4%) and 2 of them have received two assays for a total of 20 assays (20/1057; 2%). Among the 444 women, 23 (5%) had (more than 1 year before the assay) a personal history of bilateral salpingo-oophorectomy (BSO), for these patients a total of 30 assays (range: 1–3 per patient) have been performed. A total of 50 (5%) CA 125 assays were performed for men or women without annexa.

3.4. Price

The total charge for a CA 125 assay including the test, the medical and administrative costs is €46 (74 Swiss francs). Using a total of €46, €48 622 may be estimated for the 1057 samples performed. If we consider as appropriate only the samples performed for monitoring of OC ($n=537$) and as preoperative tests of an ovarian mass ($n=68$), this corresponds to a total of 605 tests with a total cost of €27 830. For all other inadequate or inappropriate indications the amount spent corresponds to €20 792 or €8604/year. If we project our results to a nationwide estimation (population in 1995 of 7 062 354), the amount spent for an inappropriate use of CA 125 test is €539 881 or €223 399/year.

4. Discussion

The aim of our study was to provide an overview of how CA 125 tests are used in routine clinical practice. If we consider as acceptable for use the CA 125 assay performed in the situations previously defined, a total

Table 1
Number of CA 125 assessments done for incorrect indications ($n=452$) and identification of the clinical problems for ordering these tests

Clinical problems	*n* (%)
Breast disease (breast cancer, mastitis, breast abscess)	74 (16)
Abnormal vaginal bleeding (uterine cancer, menstruation disorders)	56 (12)
Research on the origin and nature of a process:	46 (10)
Skin mass or ulcer or subcutaneous tumour ($n=11$)	
Liver mass or/and presence of ascitic fluid ($n=9$)	
Lung mass or/and pleural effusion ($n=9$)	
Bone pathological fracture and/or lesions on X-ray ($n=8$)	
Brain mass ($n=7$)	
Inguinal mass ($n=2$)	
Abdominal pain and/or gastrointestinal symptoms (digestive inflammation, digestive cancer, leiomyoma, abdominal abscess)	31 (7)
General symptoms (anaemia, unexplained weight loss, jaundice, unspecified symptoms)	12 (3)
Abnormal Papanicolaou test (cervical cancer, dysplasia, polyps)	6 (1)
Information not available	177 (39)
Other situations:	
Women without adnexa	30 (7)
Men	20 (4)

of 605 (57%) tests may be appropriate. Monthly evaluations of the tumour response in patients having chemotherapy were well followed by the physicians, probably because these tests are requested by medical oncologists prior to every new cycle of chemotherapy in a standardised way. In the follow-up of patients after primary treatment in order to detect a relapse, the test was used in a heterogeneous fashion, probably because its utility in this condition is controversial. The doubling of CA 125 from the upper limit of normal predicts recurrence with a specificity of 98%, sometimes weeks or months before clinical and radiological evidence of relapse. However, the clinical benefit of this lead-time is not established. It is unknown if there is any benefit of early re-introduction of chemotherapy before the appearance of radiological or clinical manifestations [13,17]. For these reasons it has been suggested that CA 125 should not be routinely requested during follow-up, but only measured to confirm recurrence. However, the current practice is generally to check these patients every 3–4 months with a clinical exam. and a CA 125 testing. In our study we have found a great variance in the use of CA 125 during follow-up, which reflects the absence of formal recommendations. In our data, some patients had only one assay over the 29-month period and others had one assay every month. We have no precise information as to why some patients had many tests and others only one.

In the case of the patients having no OC and no surgical investigation of an ovarian mass, the following observations may be made. First of all, we have found many cases (25%) in which the serum CA 125 assay values were falsely positive. Markedly elevated values (>1000 U/ml) were found in cases of abdominal ascites, pleural effusion and liver disease such as cirrhosis. These findings confirm the relatively high false-positive rate and the low specificity that we can expect from this tumour marker. Secondly, many CA 125 were requested in patients with non specific symptoms such as pelvic pain, weight loss or anaemia and patients with suspicions of skin, bone, liver, lung, brain or lymphatic tumours. We assume that physicians use the test as a tool in the differential diagnosis of the underlying disease. Such indications are probably inappropriate, because it is currently well established that CA 125 is not an immunohistochemical marker that is entirely site-specific. As a result, it will not provide useful information, either about the benign or malignant nature of the disease or the origin of the process. Even the combined use of various serum markers is probably not a reliable diagnostic strategy to accurately determine the site of origin of a metastatic cancer. Thirdly, many CA 125 determinations have been requested for screening OC in breast cancer or breast cancer relapse patients. These patients may be considered as a 'higher risk' group for OC than the general female population, however, there is as yet no conclusive evidence to recommend screening of these patients. CA 125 will therefore not provide useful information about the ovarian status. Moreover, CA 125 can be elevated in a great number of patients with metastatic breast cancer without ovarian disease [18]. Finally, an unexpected and disturbing finding was that men have received CA 125 tests, as have women without adnexa. We can probably never fully understand why these physicians have requested these tests but it seems reasonable to postulate that they simply do not know the indications of the CA 125 test.

There are as yet no scientific data available to support any form of OC screening by CA 125 determination, but we have clearly found that many CA 125 tests are performed for screening in different clinical scenarios. Until now, we have a free hand in the use of this test and clearly excessive testing is commonly seen. The question is why there is such overtesting and how to prevent it. The diagnostic uncertainty, the simple availability of the test, the pressure from patients and their family, the fear of missing a cancer and the risk of malpractice claims are possible reasons that explain excessive testing. When cancer is a possible diagnosis, the overuse of tumour markers is probably widespread and we would probably find similar results with other tumour markers. The true cost of inappropriate use with CA 125 is estimated at €8604 annually and a nationwide projection estimates an amount of €223 399 annually. One can ask how long the payers (government, insurers and patients) will continue to pay. If testing is severely restricted and paid only where the scientific data supports the indication, our ability to evaluate our patients would probably be unchanged. Therefore physicians should take note of the evidence supporting the use of CA 125 and should stop ordering tests which have no clinical utility. Moreover, an inappropriate use with a falsely positive test is not without consequences and may have some potential adverse effects such as emotional stress for the patients and their families and extensive and costly investigations to rule out OC.

In conclusion, there is evidence that a high rate of inappropriate CA 125 testing occurs in routine medical practice. Such tests are expensive and the evaluation of false-positive results adds to these costs. In the debate about health costs such elements must be taken in consideration perhaps by providing educational actions, practice guidelines and precise algorithms to the laboratory users in order to help the physicians to develop a more rational approach.

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