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Increased incidence of cancer in the follow-up of obstetric antiphospholipid syndrome within the NOH-APS cohort

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ABSTRACT

Malignancies can be associated with positive antiphospholipid antibodies but the incidence of cancer among women with the purely obstetric form of antiphospholipid syndrome (APS) is currently unknown. Our aim was to investigate the comparative incidence of cancers in women with a history of obstetric APS within a referral university hospital-based cohort (NOH-APS cohort). We performed a 17-year observational study of 1,592 non-thrombotic women with three consecutive spontaneous abortions before the 10th week of gestation or one fetal death at or beyond the 10th week of gestation. We compared the incidence of cancer diagnosis during follow-up among the cohort of women positive for antiphospholipid antibodies (n=517), the cohort of women carrying the *F5* rs6025 or *F2* rs1799963 polymorphism (n=279) and a cohort of women with negative thrombophilia screening results (n=796). The annualized rate of cancer was 0.300% (0.20%-0.44%) for women with obstetric APS and their cancer risk was substantially higher than that of women with negative thrombophilia screening [adjusted hazard ratio (aHR) 2.483; 95% confidence interval (CI) 1.27-4.85]. The computed standardized incidence ratio for women with obstetric APS was 2.89; 95% CI: 1.89-4.23. Among antiphospholipid antibodies, lupus anticoagulant was associated with incident cancers (aHR 2.608; 95% CI: 1.091-6.236). Our cohort study shows that the risk of cancer is substantially higher in women with a history of obstetric APS than in the general population, and in women with a similar initial clinical history but negative for antiphospholipid antibodies.

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Introduction

A number of case reports describe the association of antiphospholipid (aPL) antibodies with hematologic and solid organ malignancies.[1] Especially in elderly patients, thrombotic events associated with aPL antibodies can be the first manifestation of malignancy.[1] Cancer-associated monoclonal gammopathy of the IgM type can be accompanied by positive lupus anticoagulant (LA) or an anticardiolipin (aCL) IgM.[2] Cancer and antiphospholipid antibody syndrome (APS) can coexist in sporadic cases, while some cancer patients with or without thrombosis may show transient positivity for aPL antibodies;[3] the most striking symptomatic clinical feature, catastrophic APS, has been described in cancer patients.[4]

Some reports suggest a significant incidence of malignancies in APS patients. Cancer was the second cause of death (13.9%), after bacterial infection, during the 10-year follow-up of 1,000 APS patients studied by the Euro-Phospholipid Project

Group.[5] However, since no control group was simultaneously evaluated, the risk of cancer in patients with APS is still uncertain.

The Nîmes Obstetricians and Hematologists APS (NOH-APS) study[6] was based on the recruitment of a cohort of women with no history of thrombosis, who had experienced pregnancy loss fulfilling the clinical criteria of obstetric APS, who were either positive for aPL antibodies (APS group), or positive for the *F5* rs6025 or *F2* rs1799963 polymorphism (Thrombophilia group), or negative for thrombophilia screening (Control group). This provided us with the opportunity to prospectively assess the comparative incidence of cancer in women who had been diagnosied with obstetric APS. This evaluation was carried out during the 2017 medical follow-up step, corresponding to a median follow-up of 17 years. We used an external, local population-derived control group, the registry of tumors in Montpellier area (*Registre des Tumeurs de l'Hérault*), to compute standardized incidence ratios.

Methods

Study design and patients

The NOH-APS study is a referral university hospital-based, longitudinal cohort study which was initiated in 1995, with an inclusion period lasting 10 years. The recruitment is presented in Figure 1 and has been described in detail elsewhere.[6,7-10] Patients were classified as having had primary pregnancy loss (no previous successful pregnancy) or secondary pregnancy loss. The results of thrombophilia screening generated (i) an APS group of 517 women with only canonical aPL antibodies: LA, aCL IgM antibodies (aCL-M), aCL IgG antibodies (aCL-G), anti-β2GP1 (aβ2GP1) IgM antibodies (aβ2GP1-M) or aβ2GP1 IgG antibodies (aβ2GP1-G)[6]; (ii) a Thrombophilia group of 279 women with isolated *F5* rs6025 or *F2* rs1799963 polymorphism; and (iii) a Control group of 796 women.

The patients have undergone clinical re-evaluation annually in our outpatient department. The loss of patients to follow-up (n=23: 1.44%) was minimized by directly contacting the general practitioners and the patients themselves. Symptoms were evaluated and the treatments taken during the year were recorded.

The management of the women included has already been detailed.[6-10] APS patients received chronic primary thromboprophylaxis, i.e. low-dose aspirin (100 mg/day).

The study protocol and consent forms were approved by the Institutional Review Board of the University Hospital of Nîmes and the appropriate ethics committee (the local *Comité de Protection des Personnes Participant à la Recherche Biomédicale*). This clinical investigation was performed in accordance with the Helsinki Declaration, as formulated in 1975 and revised in 1996. All the women gave informed consent to participation. The study was declared to the *Commission Nationale de l'Informatique et des Libertés* (CNIL) under the number 2150873 v 0.

Outcome data

The incidence of a cancer diagnosis was the primary outcome. After questioning the patients and having performed their clinical examination, clinical details were obtained from the women's medical charts and details were verified with the medical, surgical and oncological teams involved in the diagnosis and treatment of the various incident cancers, both in our University Hospital and, for a minority, in the external relevant medical institutions that had assumed care.

Details of the statistical analysis can be found in the *Online Supplementary Material.*

Results

The analyses included 1,592 women with no initial history of thrombosis but a history of unexplained pregnancy loss (recurrent abortions or fetal death), categorized according to the results of thrombophilia screening, who collectively contributed data for a total of 26,588 person-years.

The characteristics of the patients at baseline and at follow-up evaluation are presented in Table 1. Women in the Control group initially had an obstetric history including more recurrent abortions, women in the APS group more often had an inflammatory disease and women in the Thrombophilia group more often had a family history of venous thromboembolism (VTE) or of atherothrombosis. The mortality rate was higher among women in the APS group: this was true for both global mortality, and also death from non-cancer-related causes (catastrophic APS in 1, pulmonary embolism in 2, stroke in 3, myocardial infarction in 3, viral infection in 4, bacterial infection in 8). Women in the APS group also more often developed an inflammatory non-cancerous disease (systemic lupus erythematosus in 47, rheumatoid arthritis in 7, systemic sclerosis in 4, inflammatory bowel disease in 3, ANCA-associated vasculitis in 2, sarcoidosis in 1). Focusing on the obstetric histories after inclusion into the cohort, fewer women in the APS group delivered at least one living neonate, and a higher percentage of them had a stillbirth, experienced a neonatal death, developed a placenta-mediated complication during one of their pregnancies, had to be admitted into an intensive care unit due to pregnancy complications, or delivered a neonate who had to be admitted into a specific intensive care unit. Focusing on vascular events that were diagnosed after inclusion into the cohort, a higher percentage of women in the APS group had VTE (distal or proximal deep vein thrombosis, pulmonary embolism) despite primary thromboprophylaxis using low-dose aspirin. The rate of superficial vein thrombosis was also higher in this group. Furthermore, these women more often developed arterial thrombotic events (transient ischemic attacks/strokes and myocardial infarction).

A diagnosis of cancer was made in 52 women, the annualized rate of cancer being computed as 0.20% [95% confidence interval (95% CI): 0.15%-0.26%] in the whole cohort. We observed 29 breast cancers, seven colon cancers, four pancreatic cancers, three non-Hodgkin lymphomas, three thyroid cancers, three endometrial cancers, two primary brain tumors and one lung cancer. Table 2A presents the incidence of cancer in the three groups of women: the risk of a cancer diagnosis was higher in the APS group than in the Control group, whereas it was not statistically different between the Thrombophilia group and the Control group. The incidence of cancer diagnosis remained significantly higher in the APS group than in the merged Control and Thrombophilia groups: hazard ratio (HR) 2.07 (95% CI: 1.30-3.57). The comparison between the APS and Thrombophilia groups did not reveal a statistically significant difference (HR 1.73; 95% CI: 0.78-3.81). The analysis adjusted (aHR) for characteristics of the women at inclusion and during follow-up (Table 2B) showed results similar to those of the unadjusted analysis (APS group: aHR 2.26; 95% CI: 1.20-4.24; *P*=0.0115). The Kaplan-Meier estimates of cancer-free survival among women are shown in Figure 2: the log-rank test revealed a statistically significantly increased incidence of cancers in women in the APS group.

Among women in the APS group, 64 (12.4%) developed

an inflammatory disease, whose treatment is based on drugs suspected to increase the risk of cancer (methotrexate, cyclophosphamide…), as it has been reported that cancer rates are increased in patients with systemic lupus erythematosus. Only one of these women developed a cancer during the follow-up (HR 0.74; 95% CI: 0.10-5.54).

Standardized incidence ratios of cancer were calculated: for the whole cohort (2.00; 95% CI: 1.49-2.62), the APS group (2.89; 95% CI: 1.89-4.23), the Thrombophilia group (1.60; 95% CI: 0.69-3.15) and the Control group (1.49; 95% CI: 0.89-2.37).

Focusing on the APS group, we studied the association between aPL antibodies and incident cancers, adjusted for the age of the women at inclusion. Initial positivity for LA

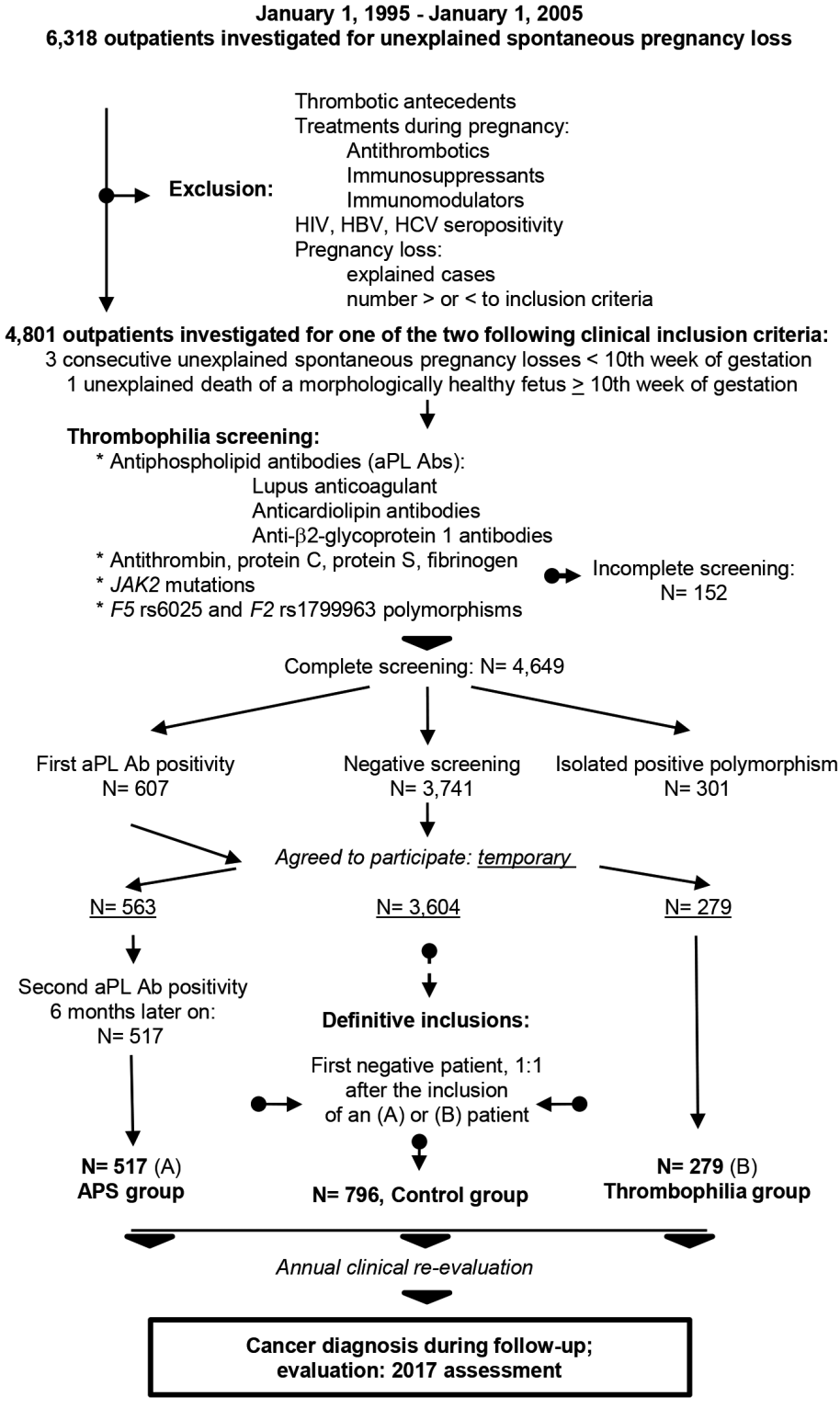

Figure 1. Flow diagram of patients in the NOH-APS cohort and its three groups. HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; aPL Ab: antiphospholipid antibody; APS: antiphospholipid syndrome

Table 1. Characteristics of the patients at baseline and at follow-up.

	Control grou	Thrombophilia group	APS group
Number	796	279	517
BASELINE			
Age, years	30 (5) [17-44]	29 (4) [18-44]	29 (4) [16-41]
Age >35 years	43 (5.4%)	12 (4.3%)	15 (2.9%)
Body mass index, kg/m^2	25.6 (4.5) [15.3-36.1]	25.9 (4.2) [13.5-34.1]	26.0 (4.6) [15.3-37.0]
>30	78 (9.8%)	29 (10.4%)	60 (11.6%)
<18.5	12 (1.5%)	3 (1.1%)	5 (1%)
Ethnicity			
Caucasian-European	647 (81.3%)	227 (81.4%)	420 (81.2%)
Caucasian-North African	106 (13.3%)	37 (13.2%)	69 (13.4%)
Black African	36 (4.5%)	12 (4.3%)	22 (4.2%)
Asian	7 (0.9%)	3 (1.1%)	6 (1.2%)
PL subtype			
Embryonic PL at <10 WG	483 (60.7%)	93 (33.3%)	206 (39.8%)
Fetal PL at ≤10 WG	313 (39.3%)	186 (66.6%)	311 (60.2%)
Primary PL	549 (68.9%)	185 (66.3%)	342 (66.1%)
Secondary PL	247 (31.1%)	94 (33.7%)	175 (33.9%)
Inflammatory disease	7 (0.9%)	4 (1.4%)	32 (6.2%)
Risk factors for vascular diseases			
Varicose veins	187 (23.5%)	58 (20.8%)	117 (22.6%)
Current smoker	83 (10.4%)	30 (10.8%)	50 (9.7%)
Hypertension	19 (2.4%)	8 (2.9%)	17 (3.3%)
Hypercholesterolemia	42 (5.3%)	13 (4.7%)	31 (6.0%)
Hypertriglyceridemia	34 (4.3%)	11 (3.9%)	27 (5.2%)
Diabetes mellitus	11 (1.4%)	2 (0.7%)	6 (1.2%)
Positive history in a first-degree relative			
Venous thromboembolism	15 (1.9%)	29 (10.4%)	12 (2.3%)
Atherothrombosis	96 (12.1%)	46 (16.5%)	53 (10.3%)
Prevalence of thrombophilia laboratory markers			
Positive for LA	0	0	319 (61.7%)
Positive for aCL-G	0	0	244 (47.2%)
Positive for aCL-M	0	0	372 (71.9%)
Positive for aβ2GP1-G	0	0	114 (22.1%)
Positive for aβ2GP1-M	0	0	210 (40.6%)
Positive for LA+aCL+ aβ2GP1	0	0	149 (28.8%)
Positive for *F5* rs6025	0	176 (63.1%)	11 (2.1%)
Positive for *F2* rs1799963	0	103 (36.9%)	6 (1.2%)
FOLLOW-UP *(data obtained during the last evaluation)*			
Follow-up duration, days	6209 (1758) [371-8029]	6166 (1770) [1294-8011]	6251 (1768) [1085-8030]
Lost to follow-up	23 (2.9%)	8 (2.9%)	6 (1.2%)
Deceased	13 (1.6%)	5 (1.8%)	29 (5.6%)
Deceased, *non-cancer-related*	8 (1.0%)	4 (1.4%)	21 (4.1%)
Age, years	46 (7) [27-64]	46 (6) [32-63]	46 (7) [30-61]
Body mass index, kg/m^2	27.8 (4.7) [17.4-41.1]	27.6 (4.5) [17.9-40.5]	28.0 (4.9) [18.1-40.8]
>30	121 (15.2%)	44 (15.8%)	82 (15.9%)
<18.5	31 (3.9%)	12 (4.3%)	20 (3.9%)
Cancer history, first-degree relatives	164 (20.6%)	52 (18.6%)	114 (22.1%)
Current smokers	237 (29.8%)	89 (31.9%)	163 (31.5%)
Inflammatory disease	23 (2.9%)	10 (3.6%)	64 (12.4%)
Diabetes mellitus	27 (3.4%)	10 (3.6%)	21 (4.1%)
Number of new pregnancies	2 [1-3]	2 [1-3]	2 [1-4]
Outcomes of new pregnancies			
At least one living neonate	695 (87.3%)	233 (83.5%)	417 (80.7%)
Embryonic PL <10 WG	297 (37.3%)	96 (34.4%)	198 (38.3%)
Fetal death ≥10 WG	101 (12.7%)	37 (13.3%)	85 (16.4%)
Stillbirth	36 (4.5%)	15 (5.4%)	46 (8.9%)
Neonatal death	12 (1.5%)	6 (2.2%)	27 (5.2%)

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	Control grou	Thrombophilia group	APS group
Placenta-mediated complications	139 (17.5%)	62 (22.2%)	149 (28.8%)
ICU admission, patient	48 (6.0%)	23 (8.2%)	67 (12.9%)
ICU admission, neonate	67 (8.4%)	37 (13.3%)	89 (17.2%)
Venous thrombosis			
All deep events	59 (7.4%)	27 (9.7%)	129 (24.9%)
Deep vein thrombosis, all	59 (7.4%)	27 (9.7%)	129 (24.9%)
Deep vein thrombosis, distal	23 (2.9%)	6 (2.2%)	47 (9.1%)
Deep vein thrombosis, proximal	36 (4.5%)	21 (7.5%)	82 (15.9%)
Pulmonary embolism	17 (2.1%)	6 (2.2%)	38 (7.4%)
Superficial vein thrombosis	20 (2.5%)	18 (6.5%)	40 (7.7%)
Arterial thrombosis			
All events	21 (2.6%)	15 (5.4%)	49 (9.5%)
Transient ischemic attack / stroke	14 (1.8%)	10 (3.6%)	30 (5.8%)
Myocardial infarction	5 (0.6%)	3 (1.1%)	11 (2.1%)
Antithrombotic treatments, last evaluation			
Low-dose aspirin	9 (1.1%)	6 (2.2%)	362 (70%)
Thienopyridine	21 (2.6%)	15 (5.4%)	84 (16.2%)
Vitamin K antagonists	0	0	120 (23.2%)
Direct oral anticoagulants	35 (4.4%)	20 (7.2%)	0
Low-molecular weight heparin	1 (0.1%)	1 (0.4%)	5 (1%)

Quantitative data are given as median (interquartile range) [range] and qualitative data as number (percentage) values. APS: antiphospholipid syndrome; PL: pregnancy loss; WG: weeks of gestation; LA: lupus anticoagulant; aCL: anticardiolipin; ICU: intensive care unit

was the only aPL antibody found to be significantly associated with incident cancers (Table 3).

As the aPL antibodies did not always remain positive during follow-up, we studied the association with individual exposures to positive aPL antibodies during the follow-up, that is, the "E" parameter, which, for each of the five aPL antibodies, is the sum of all the annual positivities throughout the duration of the follow-up (Table 4). Only exposure to LA was associated with incident cancers.

We also explored the association between the strength of the antibody titers and the risk of cancer, studying intensities of exposure to aPL antibodies during the follow-up, that is, the "IE" parameter, which, for each of the five aPL antibodies, is the sum of the corresponding positive antibody titers throughout the duration of the follow-up (Table 5). Only intensity of exposure to LA was associated with incident cancers.

A total of 14 women developed symptomatic VTE before a diagnosis of cancer: nine in the APS group, two in the Thrombophilia group and three in the Control group. These cases accounted for a minority of all cases of VTE (n=215) observed during the follow-up of the cohort [14/215: 6.5% (3.9%-10.6%)]. In six cases, VTE occurred in the 100 days preceding the diagnosis of cancer, and was thus considered to be related to the malignancy (4 pancreatic cancers and the 2 primary brain tumors). In our population, incident VTE was a limited global indicator of an underlying cancer [6/52: 11.5% (5.4%-22.9%)], but was associated with types of cancer known to activate the hemostatic system strongly.

Discussion

In this exploratory analysis of long-term follow-up data from a cohort of women with a personal history of pregnancy loss categorized according to the results of thrombophilia screening, a diagnosis of obstetric APS was associated with a higher rate of incident cancers than the rate in women with negative thrombophilia screening. The risk of a diagnosis of cancer was influenced by age, body mass index, development of diabetes mellitus during follow-up and evidence of atherothrombosis in a first-degree relative. The risk of cancer was associated with positivity for LA, not with anti-β2GP1 antibodies, both in terms of initial positivity at inclusion and in terms of cumulative exposure to this aPL antibody during follow-up. The risk was not associated with positivity for anti-β2GP1 antibodies.

We did not observe a significantly increased cancer risk in the APS group compared to that in the Thrombophilia group. However, this latter group was the smallest, thus limiting the capacity to detect significant differences, since there was a clear lack of statistical power for detecting moderate differences. For the same reason, we cannot definitely exclude that the risk of incident cancer in women positive for the *F5* rs6025 or *F2* rs1799963 polymorphism is slightly higher than that in women with negative thrombophilia screening, intermediate between the risk in the Control group and the risk in the APS group. Finally, the mean standardized incidence ratio of cancer was close to 1.5 in the Control group, but was not significant. Here also, we paid the price of a lack of statistical power. A huge retrospective population-based study in the southern district of Israel, which included 106,265 patients with a history of two or more consecutive pregnancy losses and a mean follow-up of 12 years, evidenced an aHR of 1.4 for the future risk of female malignancies.[12] Part of the association between aPL antibodies and the increased risk of incident cancers may thus be related to the unfavorable obstetric outcomes. However, in women sharing the same initial clinical history, aPL antibodies were associated with an increased risk.

A recent systematic review and meta-analysis of data from individual patients showed that occult cancer is detected in around one in 20 patients within a year of

receiving a diagnosis of unprovoked VTE.[13] The data from our cohort are of the same order of magnitude [6/178: 3.4% (1.6%-7.2%)]. Of interest, most of the VTE events observed in our cohort were unprovoked [178/215: 82.8% (77.2%-87.3%)], probably because systematic thromboprophylaxis with low molecular weight heparin was proposed to the women in the Thrombophilia and APS groups, known to be more prone to VTE in the case of an intercurrent risk factor for thrombosis. Another point is that women in the APS group received primary thromboprophylaxis with low-dose aspirin, which may have affected the rate of unprovoked events in that group. We cannot, therefore, consider that the thrombotic events observed within our cohort reflect a natural pattern of evolution.

There is now clear evidence that chronic low-dose aspirin treatment can prevent one-third of colorectal, gastric, and esophageal cancers,[14] and possibly some other types of cancer.[15] Preclinical and clinical studies show that tumorigenesis and metastasis can be promoted by platelets through a wide variety of crosstalk between platelets and cancer cells.[16] It is thus likely that the incidence of cancer in our APS group does not correspond to the natural evolution of that group, and that the panel of cancer types developed by the women with APS is not the natural panel. The potentially protective effect of chronic low-dose aspirin treatment does, however, reinforce the finding of a higher incidence of cancers in the follow-up of APS women, and adds support to a wider use of this non-consensual care.

The β2GP1/anti-β2GP1 autoantibody progressively becomes the dominant one in thrombotic APS,[17] albeit with some remaining uncertainty in purely obstetric APS. The main finding of this observational study is the association between LA and incident cancers; a putative association with anti-β2GP1 autoantibody did not reach statistical significance. This could of course be the consequence of a lack of statistical power, positive anti-β2GP1 autoantibodies being less prevalent in our women with obstetric APS. It is also possible that the type and strength of aPL antibodies influence the appearance of incident cancer in positive women, in terms of both the types of cancer and in the differential levels of risk. Our study cannot resolve this issue. A more complex model may be needed to explain why some aPL antibodies did not appear to have an effect in this limited first analysis. A further possibility is that another aPL antibody cofactor, not β2GP1, may better explain the increased incidence of cancer in our women with APS. The most likely candidate for further investigation is coagulation factor II (prothrombin), because of the impact of LA.[18]

The association between aPL antibodies and the increased incidence of cancers is difficult to interpret. There is currently no definitive demonstration of an association between chronic hypercoagulability and the risk of cancer, although one prospective study showed that men with higher levels of prothrombin fragments 1+2 had an increased risk of digestive tract cancers during a 10-year follow-up.[19] At the phenotypic level, circumstantial evidence suggests a role for coagulation factors, particularly tissue factor and thrombin, in the signaling pathways of tumorigenesis (e.g., angiogenesis, apoptosis, evasion, invasion, and metastasis).[20-23] Some polymorphisms in the *F5*, *F7*, *F10*, *F13A*, and *PROCR* genes, whose effects on the coagulation phenotype are not fully characterized, are associated with the risk of solid tumors;[24] for instance, breast cancer is associated with polymorphisms in the *F5*, *F10* and *PROCR* genes.[25] However, the aPL antibody most significantly associated with incident cancers (i.e., LA)

Table 2A. Incidence of cancer in the three groups of women constituting the NOH-APS cohort. Crude data and unadjusted analysis with the Control group as the reference.

Group	Control	Thrombophilia	APS
Patient-years of follow-up	13 260.35	4 662.77	8 664.98
Cancer diagnosis: number of cases.	18*	8**	26***
Annualized rates of cancer, % (95% CI)	0.14 (0.10-0.21)	0.17 (0.09-0.34)	0.30 (0.20-0.44)
Hazard ratio 95% CI	1	1.28 (0.56-2.95)	2.22 (1.22-4.06)
P		0.56	0.0092

*APS: antiphospholipid syndrome; 95% CI: 95% confidence interval; HR: hazard ratio. *Breast cancer (n=10), colon cancer (n=3), endometrial cancer (n=2), pancreatic cancer (n=1), thyroid cancer (n=1), lung cancer (n=1). **Breast cancer (n=7), colon cancer (n=1). ***Breast cancer (n=12), non-Hodgkin lymphoma (n=3), colon cancer (n=3), pancreatic cancer (n=3), endometrial cancer (n=1), thyroid cancer (n=2), primary brain tumor (n=2).

Table 2B. Associations of clinical parameters and biological parameters in women with an incident cancer during follow-up as compared with women with no cancer.

	Univariate analysis HR (95% CI) P		Multivariate analysis** aHR (95% CI) *P*	
Clinical associations				
Inclusion:				
Age, years *	1.14 (1.06-1.22)	0.0003	1.15 (1.07-1.24)	0.0002
Body mass index, kg/m^2 *	1.10 (1.01-1.19)	0.0284	1.10 (1.01-1.20)	0.0217
Fetal death	1.08 (0.63-1.86)	0.79		
Secondary pregnancy loss	0.70 (0.40-1.21)	0.203		
Follow-up:				
Family history of cancer	0.72 (0.34-1.55)	0.41		
Family history of VTE	0.92 (0.22-3.79)	0.91		
Family history of atherothrombosis*	2.04 (1.07-3.89)	0.0300	2.47 (1.28-4.76)	0.0071
Active smoking	1.15 (0.49-2.68)	0.75		
Non-cancerous inflammatory disease	0.76 (0.11-5.52)	0.79		
Immunosuppressive treatment	0.74 (0.10-5.54)	0.76		
Diabetes mellitus*	5.46 (1.32-22.5)	0.0186	5.13 (1.16-22.7)	0.0311
Pregnancy loss	0.87 (0.49-1.55)	0.63		
Fetal death	0.82 (0.32-2.10)	0.68		
Stillbirth	0.77 (0.18-3.19)	0.71		
Neonatal death	1.35 (0.33-5.57)	0.67		
Placenta-mediated complication	1.08 (0.51-2.30)	0.84		
Venous thromboembolism	1.37 (0.67-2.80)	0.40		
Pulmonary embolism	1.58 (0.49-5.06)	0.44		
Deep vein thrombosis				
Proximal*	1.82 (0.86-3.88)	0.119		
Distal	0.45 (0.06-3.30)	0.44		
Superficial vein thrombosis*	2.13 (0.85-5.38)	0.108		
Arterial thrombosis*	2.89 (1.04-8.05)	0.0419		
Biological associations (comparator: Control group)				
APS*	2.23 (1.22-4.06)	0.0092	2.26 (1.20-4.24)	0.0115
Thrombophilia	1.28 (0.56-2.95)	0.56		

HR: hazard ratio; 95% CI: 95% confidence interval; aHR: adjusted hazard ratio; VTE: venous thromboembolism; APS: antiphospholipid syndrome. *Variables included in the multivariate analysis. **Likelihood ratio of the model: χ^2 41.15, 10 degrees of freedom, P<0.0001.

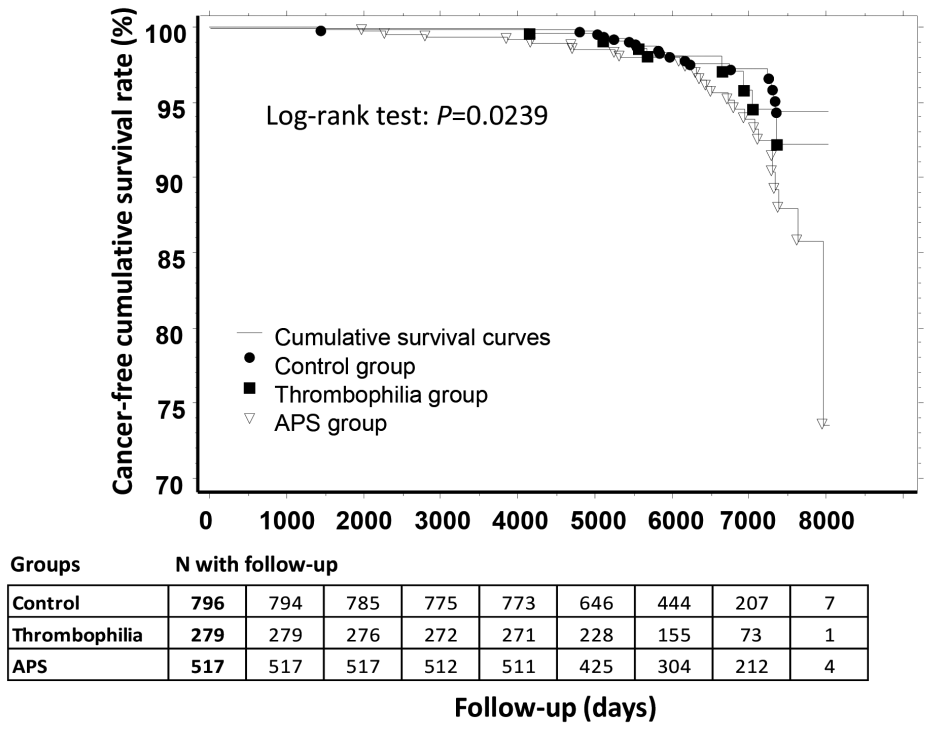

Figure 2. Cancer-free survival in the three groups of women in the NOH-APS study. APS: antiphospholipid syndrome.

was not the one currently perceived as being the most thrombogenic (i.e., aβ2GP1-G). Chronic cell activation, engagement of cell signaling pathways, modulation of cell autophagy and apoptosis, and induction of an uncontrolled inflammatory cascade are new hypotheses regarding aPL antibody-related pathogenesis, which may play a role in this association.[17,26] There is increasing evidence to suggest that patients with systemic lupus erythematosus have a slightly higher overall risk of malignancy but the underlying mechanisms remain speculative.[27] Finally, currently unidentified factors, more frequently present in patients with autoimmune diseases, may be the real culprits, for example DNA-damaging autoantibodies,[28] as well as key inflammatory chemokines and cytokines.[29]

Our study has various limitations. The first drawback of this study is that it was performed in a single center. Multicenter replication studies should be carried out to confirm its results. Second, the investigators were not

Table 3. Hazard ratios for an incident cancer according to the type of antiphospholipid antibody present at inclusion.

	aHR*	95% CI	P
Age at inclusion, per year	1.29	1.15-1.45	<0.0001
Positive aPL antibody:			
LA	2.61	1.09-6.24	0.0312
aCL-G	0.99	0.44-2.19	0.97
aCL-M	1.17	0.46-2.95	0.75
aβ2GP1-G	0.67	0.26-1.75	0.41
aβ2GP1-M	0.85	0.38-1.94	0.70

aHR: adjusted hazard ratio; 95% CI: 95% confidence interval; aPL antiphospholipid; LA: lupus anticoagulant; aCL-G: anticardiolipin IgG isotype; aCL-M: anticardiolipin IgM isotype; aβ2GP1-G: anti-β2GP1 IgG isotype; aβ2GP1-M: anti-β2GP1 IgM isotype. *For each of the five aPL antibodies, adjustment on the four others, and for age at inclusion.

Table 4. Analysis of incident cancers according to exposure to antiphospholipid antibodies during the follow-up.

	aOR*	95% CI	P
Age at inclusion, per year	1.28	1.14-1.43	<0.0001
E^{LA}	1.08	1.02-1.13	0.0061
$E^{aCL\text{-}G}$	1.01	0.96-1.06	0.79
$E^{aCL\text{-}M}$	1.04	0.98-1.10	0.22
$E^{a\beta2GP1\text{-}G}$	0.99	0.93-1.04	0.59
$E^{a\beta2GP1\text{-}M}$	1.00	0.95-1.05	0.94

For a given antiphospholipid antibody, exposure (E) is defined as the sum of all the annual positivities throughout the duration of the follow-up. aOR: adjusted odds ratio; 95% CI: 95% confidence interval; aβ2GP1-G: anti-β2GP1 IgG isotype; aβ2GP1-M: anti-β2GP1 IgM isotype; E^{LA}: exposure to lupus anticoagulant; EaCL-G: anticardiolipin IgG isotype; $E^{aCL\text{-}M}$: anticardiolipin IgM isotype; $E^{a\beta2GP1\text{-}G}$: anti-β2GP1 IgG isotype; $E^{a\beta2GP1\text{-}M}$: anti-β2GP1 IgM isotype. *For each of the five E parameters: adjustment on the four others, and on age at inclusion.

Table 5. Analysis of incident cancers according to intensity of exposure to antiphospholipid antibodies during the follow-up.

	aOR*	95% CI	P
Age at inclusion, per year	1.28	1.14-1.43	<0.0001
IE^{LA}	1.04	1.01-1.07	0.0059
$IE^{aCL\text{-}G}$	0.99	0.98-1.01	0.57
$IE^{aCL\text{-}M}$	1.03	1.01-1.07	0.0288
$IE^{a\beta2GP1\text{-}G}$	0.99	0.96-1.01	0.23
$IE^{a\beta2GP1\text{-}M}$	1.01	0.97-1.06	0.59

For a given antiphospholipid antibody, the intensity of exposure (IE) is defined as the sum of all the antibody titers of annual positivities throughout the duration of the follow-up. aOR: adjusted odds ratio; 95% CI: 95% confidence interval; IE^{LA}: intensity of exposure to lupus anticoagulant; $IE^{aCL\text{-}G}$: intensiy of exposure to anticardiolipin IgG isotype; $IE^{aCL\text{-}M}$: intensity of exposure to anticardiolipin IgM isotype; $IE^{a\beta2GP1\text{-}G}$: intensity of exposure to anti-β2GP1 IgG isotype; $IE^{a\beta2GP1\text{-}M}$: intensity of exposure to anti-β2GP1 IgM isotype. *For each of the five IE: adjustment on the four others, and on age at inclusion.

blinded to the group to which the patient was assigned. However, symptomatic cancer diagnosis leaves little room for individual interpretation. Third, incident cancers remained rare during the follow-up, occurring in only 3.3% of the women, thus limiting the potential for a more precise description of their full association with biological parameters which are not independent of each other. The very low number of symptomatic cancers that were diagnosed in our patients is a strong limitation of the study. A multicenter evaluation including a huge number of cases is necessary. Fourth, aPL antibodies may be a non-causal artifact rather than a direct risk factor.

Our study also has several strengths. It received substantial support from the NOHA administrative region-hospital medical network through which we were able to recruit a substantial number of patients. Only a very small number of patients were lost to follow-up. The primary outcome was not ambiguous and only objectively-proven clinical events and parameters were analyzed.

In summary, we found an increased incidence of cancers during the follow-up of women with pure obstetric APS, with a significant association with LA. A very large prospective, multicenter replication study is now needed. If such a study confirms our data, it would legitimate more fundamental studies to elucidate the underlying pathophysiology..

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