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ORIGINAL ARTICLE

SCCA and CYFRA 21-1 Reference Intervals for Apparently Healthy Chinese Adults: a Multicenter Cross-Sectional Study

Minglei Jiang [1, 2, *], Zhiyun Gong [1, 2, *], Jing Shen [3], Wenbing Wu [3], Ting Zhang [4], Bo Xiang [4], Falin Chen [3], Yongping Lin [4], Jiabin Shen [1], Suhong Xie [1, 2], Renquan Lu [1, 2], Lin Guo [1, 2]

[*] *Minglei Jiang and Zhiyun Gong contributed equally as first co-authors*
[1] *Department of Clinical Laboratory, Fudan University Shanghai Cancer Center, Shanghai, China*
[2] *Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*
[3] *Department of Clinical Laboratory, Fujian Provincial Hospital, Fuzhou, China*
[4] *Department of Laboratory Medicine, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*

SUMMARY

Background: **This study aimed to establish reference intervals for two biomarkers actively utilized in routine annual medical check-ups in China: squamous cell carcinoma antigen (SCCA) and cytokeratin 19 fragment (CYRFA 21-1), and to understand the influence of age, gender, and benign nodule(s) on their levels.**
Methods: **This prospective multicenter cross-sectional study continuously enrolled apparently healthy adults attending annual medical check-ups at three sites in 2019. Serum SCCA and CYFRA 21-1 levels were measured using electrochemiluminescence immunoassays. Age- and gender-specific reference intervals for the two biomarkers were established by using the 0 - 95th percentiles with 90% confidence intervals (CIs). The 97.5th percentiles were also provided.**
Results: **A total of 1,017 subjects were enrolled in this study. Both biomarkers were significantly lower in females, and age was negatively associated with SCCA while positively associated with CYFRA 21-1 (all $p < 0.0001$). No statistically significant differences were determined between subgroups without/with benign nodule(s) despite nodule(s) status (all $p > 0.05$). The overall reference interval for SCCA is 0 - 2.64 ng/mL and 0 - 4.39 ng/mL for CYFRA 21-1. The age-specific reference intervals for SCCA are 0 - 2.76 ng/mL (18 - 49 years) and 0 - 2.22 ng/mL (≥ 50 years), and for CYFRA 21-1, they are 0 - 3.86 ng/mL (18 - 49 years) and 0 - 4.89 ng/mL (≥ 50 years). The gender-specific reference intervals for SCCA are 0 - 2.83 ng/mL (male) and 0 - 2.49 ng/mL (female), and for CYFRA 21-1, they are 0 - 4.34 ng/mL (male) and 0 - 4.45 ng/mL (female).**
Conclusions: **The reference intervals for SCCA and CYFRA 21-1 established in this study could be utilized in annual medical check-ups and contribute to the screening of lung cancer in China.**
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Correspondence:
Renquan Lu
Department of Clinical Laboratory
Fudan University
Shanghai Cancer Center
270 Dongan Road, Xuhui
Shanghai
China
Email: renquanlu@fudan.edu.cn

Lin Guo
Department of Clinical Laboratory
Fudan University
Shanghai Cancer Center
270 Dongan Road, Xuhui
Shanghai
China
Email: guolin500@hotmail.com

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Supplementary Data

Table S1. The coefficient of variation (CV) for quality control of SCCA and CYFRA 21-1 measurements.

CV value	SCCA		CYFRA 21-1	
	PC * 1	PC 2	PC 1	PC 2
Site 1	1.27%	1.26%	1.87%	1.20%
Site 2	2.64%	1.53%	2.09%	2.41%
Site 3	2.22%	1.84%	2.06%	1.88%

*** PC: PreciControl Lung Cancer is used for quality control of the Elecsys SCC and CYFRA immunoassays on the Elecsys and cobas e immunoassay analyzers.**

Table S2. Site-specific demographic and baseline characteristics of the study population.

		Site 1	Site 2	Site 3	p
Age	mean (SD)	42.46 (15.73)	48.71 (12.87)	42.77 (12.56)	
	median (IQR)	37 (30 - 55)	48.5 (37.5-59)	43 (31 - 53)	< 0.0001
Subject at each age subgroup n (%)	18 - 49 years	253 (63.25)	130 (51.59)	236 (64.66)	0.0022
	≥ 50 years	147 (36.75)	122 (48.41)	129 (35.34)	
Gender n (%)	female	268 (67)	160 (63.49)	190 (52.05)	< 0.0001
	male	132 (33)	92 (36.51)	175 (47.95)	
Serum SCCA level ng/mL	mean (SD)	1.42 (0.66)	1.50 (0.81)	1.28 (0.72)	
	median (IQR)	1.28 (1.03 - 1.67)	1.35 (1 - 1.79)	1.11 (0.86 - 1.48)	< 0.0001
Serum CYFRA 21-1 level ng/mL	mean (SD)	2.34 (1.01)	2.57 (1.03)	2.50 (1.00)	
	median (IQR)	2.15 (1.66 - 2.79)	2.36 (1.9 - 3.01)	2.35 (1.73 - 3.06)	0.0013

Table S3. Site-specific reference intervals of SCCA and CYFRA 21-1 for medical check-up population in China.

		Site 1		Site 2		Site 3	
		95th	97.5th	95th	97.5th	95th	97.5th
Serum SCCA level	whole population	2.69	3.06	2.74	3.24	2.45	2.85
	Age-specific reference intervals						
	18 - 49 years	2.76	3.09	2.93	4.38	2.74	2.93
	≥ 50 years	2.28	2.99	2.42	2.86	1.75	2.17
	Gender-specific reference intervals						
	Female	2.58	3.00	2.41	2.63	2.45	2.86
	Male	2.84	3.44	3.24	3.56	2.47	2.76
Serum CYFRA 21-1 level	whole population	4.18	4.90	4.50	4.96	4.45	4.85
	Age-specific reference intervals						
	18 - 49 years	3.68	4.21	3.98	4.66	4.05	4.61
	≥ 50 years	4.96	5.96	4.93	5.34	4.72	5.46
	Gender-specific reference intervals						
	female	3.94	4.52	4.76	5.22	4.66	5.20
	male	4.96	5.96	3.92	4.71	4.09	4.47