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Asymptomatic Healthy Population With Raised CA 72-4 Has A Low Prevalence of Malignancy and Does Not Have An Increased Risk of Malignancy on Long-Term Follow-Up

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Abstract

Background and Aims: Many governments have been promoting regular health screening. The main dilemma is what to do when these asymptomatic people are found to have a raised CA 72-4. This prospective study aims to determine the prevalence of malignancy in asymptomatic people with raised CA 72-4 and, if increased CA 72-4 was associated with a higher chance of developing malignancy on long-term follow-up.

Results: One-hundred-and-thirty-one patients had raised CA 72-4 (CA 72-4 group) with 706 patients in the Control group. Seven of the 131 patients in the CA 72-4 group, compared with 24 of the 706 patients in the Control group, had malignancy at the time of recruitment (5.3 % vs. 3.4 %, respectively; p=0.279). At the 36-month follow-up, no patients in either group were detected to have malignancy [0/124 (0 %) in the CA 72-4 group vs. 0/682 (0 %) in the Control group, respectively; p=0.284)]. In the CA 72-4 group without malignancy, serial CA 72-4 showed a fluctuating CA 72-4 level in 77 of the 124 patients (62.1 %), while 47 of the 124 patients (37.9 %) had a persistently elevated CA 72-4 level. There was no significant difference in the development of malignancy at the end of follow-up when those with fluctuating CA 72-4 level [0/77 (0 %)] were compared with those with persistently raised CA 72-4 group [0/47 (0 %)] (p=1.000).

Conclusion: The prevalence of malignancy in those with raised CA 72-4 is low at only 5.3%. Increased CA 72-4 is not associated with a higher risk of developing malignancy on long-term follow-up.

Keywords: asymptomatic healthy population; longitudinal CA 72-4; long-term follow-up; raised CA 72-4; malignancy.

Introduction

Many governments in the World have been promoting a holistic approach to leading a healthy lifestyle, which includes being physically active, maintaining a balanced diet, and having regular medical screening to keep citizens healthy. However, many people, even medical professionals, are still determining what to screen. The Health Promotion Board, an agency under the Ministry of Health Singapore, provides health screening recommendations. Their offers are age-based. For example, if one is above the age of 50, this Board recommends checking for diabetes mellitus, lipid profile, blood pressure, and colorectal cancer. **[1]**

However, many people or citizens may be surprised that the recommended screening tests are so limited. The reason for such a short list of recommended diseases to screen for is that many diseases, especially cancer, cannot be screened. Furthermore, screening for cancers such as prostate cancer, stomach cancer, and pancreatic cancer is not well accepted. According to the Health Promotion Board, the only cancers that can be successfully screened are colorectal, cervical, and breast. Even then, screening for breast cancer is not without controversies, especially with the current medical advancement in treating breast cancer. **[1]**

Despite these recommendations, many medical professionals still screen for malignancies like gastric cancer using carbohydrate antigen (CA) 72-4, especially in Chinese, as part of a routine health screening. This is understandable, as gastric cancer is aggressive and fatal. It is also the fifth most common cancer in the World, with one million new cases reported each year, half of them from China.**[2]**

The main dilemma facing clinicians, especially specialists, is what to do when this group of asymptomatic healthy population is referred to them for an incidental finding of raised CA 72-4. Do they observe since these people are asymptomatic, or do they investigate, as CA 72-4 has been reported to have a high specificity of 92.8 % for gastric cancer? **[3]** If they do investigate, do they perform an esophagogastroduodenoscopy (EGD), or do they investigate further if the EGD is unremarkable as CA 72-4 is also expressed in human adenocarcinomas like colonic, breast, ovarian, cervical, endometrial and lung malignancies. **[4-8]** To decide on the best management

approach for this group of asymptomatic healthy population incidentally found to have a raised CA 72-4, there is a need to determine the prevalence of malignancy and clinical course in this group.

Methods

Subjects and Design

All consecutive Chinese asymptomatic healthy people referred to the Center for Digestive Diseases from February 2009 to May 2019 for raised CA 72-4 (CA 72-4 group) were recruited into this prospective study.

Patients with a history of solid organ malignancy, hematological malignancy, pancreatic pathology, autoimmune diseases, tuberculosis, liver cirrhosis, chronic rheumatic heart diseases, or serum creatinine of more than 160 μmol/L were excluded from the study.

Control Group

All consecutive Chinese patients with two successive normal CA 72-4 tested two months apart undergoing EGD during the same endoscopy session as those with raised CA 72-4 were recruited as the Control group.

Investigation

EGD was performed on all CA 72-4 patients and Control groups. If the EGD does not reveal any evidence of gastric cancer, the patients will have a colonoscopy, a low-dose computerized tomography (CT) of the thorax, and magnetic resonance imaging (MRI) of the abdomen and pelvis (plain and contrast). An ultrasound of the breasts and a mammogram were performed on all female patients in both groups.

EGD

EGD (Olympus, Tokyo, Japan) was performed with conventional white-light and Narrow Band Imaging under conscious sedation with intravenous midazolam and pethidine. All patients were fasted for more than eight hours before EGD.

All patients undergoing EGD had helicobacter pylori checked with both a Rapid Urease Test (CLO test; Halyard Sales, Alpharetta, Georgia, USA) and histologically for helicobacter pylori status by hematoxylin and eosin stains and Giemsa stain from two blind biopsies taken from the antrum and corpus as previously described. **[9,10]** Helicobacter pylori was identified by its curved-shaped morphology, located on the epithelial cell surface within the gastric pits or the overlying mucus layer, and by positive results on Giemsa staining. Patients were helicobacter pylori positive when the rapid urease test and histology were positive for helicobacter pylori. **[9,10]** Biopsy tissues were also examined for histological evidence of atrophic gastritis and intestinal metaplasia.**[10]**

Colonoscopy

Colonoscopy was performed with conventional white-light colonoscopy (Olympus, Tokyo, Japan) under conscious sedation with intravenous midazolam and pethidine as previously described. **[11,12]**

CA 72-4 testing

CA 72-4 serum was tested with the Roche Diagnostics Cobas CA72–4 kits on the Roche Cobas e411 (Roche Diagnostics, Rotkreuz, Switzerland). The normal cut-off was defined as < 6 U/ml.

Follow-up

Patients in the CA 72-4 group diagnosed with malignancy at the time of recruitment were followed up for 12 months with serial monitoring of CA 72-4 every three months. They would have an 18F-fluorodeoxyglucose (18FDG) whole body positron emission tomography-computerized tomography (PET-CT) ± colonoscopy (for those diagnosed with colorectal cancer) at 6 and 12 months of follow-up to look for recurrence of the tumor.

Those without malignancy in both groups at the time of recruitment were prospectively followed up for a period of 36 months. Serial CA 72-4 was performed every 6 months. An EGD, colonoscopy, low dose CT thorax, and MRI of the abdomen and pelvis (plain and contrast) were repeated at the end of the 36-month follow-up period in those without malignancy found at the time of recruitment. All female patients had a breast ultrasound, and a mammogram was repeated at the end of the follow-up.

Those diagnosed with malignancy at the time of recruitment in the Control group were discontinued from the study.

The primary aim of this study was to determine the prevalence of malignancy in an asymptomatic healthy population incidentally found to have raised CA 72-4 during routine health screening. The secondary aim of this study was to determine if presented CA 72-4 was associated with a higher chance of developing malignancy on prospective follow-up in this group of asymptomatic healthy population.

This study was approved by the Institutional Review Board of the Centre for Digestive Diseases (Protocol approval number CDD09-00003). Written informed consent was obtained from all patients for EGD, colonoscopy, CT, MRI, mammogram, ultrasound of the breasts, PET-CT, and follow-up.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, New York, USA). The Mann-Whitney U-test was used for continuous variables with skewed distribution and chi-square with Yates' correction factor or Fisher's exact test for categorical variables. Continuous variables were expressed as median (range). All statistics were performed to treat the population. Statistical significance was defined as $p < 0.05$ (two-tailed).

Results

Study population

A total of 131 consecutive patients were recruited into the CA 72-4 group, with 706 straight patients recruited into the Control group. The baseline demographics of the two groups are shown in Table 1.

There was no significant difference in the baseline demographics between the CA 72-4 and Control groups (all p< 0.05, respectively) **[Table 1]**.

Table 1. Baseline demographics of patients in the CA 72-4 and Control group.

	CA 72-4 group (n=131)	Control group. (n=706)	P-value
Age, years (range)	52.3 (26.1-75.3)	53.3 (25.6-86.3)	0.19
Sex, M: F	79: 52	365: 341	0.070
Body mass index, kg/m^2	23.4 (17.6-41.4)	23.4 (18.2-41.9)	0.894
Smoking:			0.979
Yes	14 (10.7 %)	76 (10.8 %)	
No	117 (89.3 %)	630 (89.2 %)	

CA 72-4 and EGD findings

The EGD findings in the CA 72-4 and Control groups are shown in Table 2. Patients in the CA 72-4 group were more likely to have a normal EGD when compared with those in the Control group (p< 0.001) [Table 2]. There was a trend that the CA 72-4 group had a lower chance of gastric intestinal metaplasia on EGD (p= 0.056) **[Table 2]**.

Table 2. Finding on esophagogastroduodenoscopy

	CA 72-4 group (n=131)	Control group. (n=706)	P-value
Normal EGD	79 (60.3 %)	306 (43.3 %)	<0.001
Gastritis	17 (13.0 %)	99 (14.0 %)	0.750
Reflux esophagitis	3 (2.3 %)	27 (3.8 %)	0.254
Cancer of stomach	0 (0 %)	3 (0.4 %)	0.606
Gastric ulcer	4 (3.1 %)	45 (6.4 %)	0.137
Atrophic gastritis	0 (0 %)	1 (0.1 %)	0.183
Duodenal ulcer	0 (0 %)	9 (1.3 %)	0.615
Helicobacter pylori infection	15 (11.5 %)	95 (13.5 %)	0.389
Gastric intestinal metaplasia	9 (6.9 %)	90 (12.7 %)	0.056
Gastric erosion	4 (3.1 %)	17 (2.4 %)	0.664
Barrett's esophagus	0 (0 %)	4 (0.6 %)	0.794
Gastrointestinal stromal tumor	0 (0 %)	2 (0.3 %)	0.402
Esophageal varices	0 (0 %)	1 (0.1 %)	0.183
Cancer of esophagus	0 (0 %)	1 (0.1 %)	0.183
Esophageal ulcer	0 (0 %)	6 (0.8 %)	0.927

Malignancy at the time of recruitment

A total of 31 patients were diagnosed to be suffering from malignancy at the time of recruitment. The malignant pathologies diagnosed in both groups are listed in **Table 3**.

Seven of the 131 patients (5.3 %) in the CA 72-4 group, compared with 24 of the 706 patients (3.4 %) in the Control group, were found to have a malignancy at the time of recruitment.

Patients in CA 72-4 group did not have a significantly higher chance of malignancy at the time of recruitment when compared with the Control group (p= 0.279).

Table 3: List of malignancy.

	CA 72-4 group (n=131)	Control group (n=706)	P-value
Total malignancy diagnosed	7 (5.3 %)	24 (3.4 %)	0.138
Cancer of lung	3	2	
Colorectal cancer	2	0	
Endometrial cancer	1	1	
Cancer of breast	1	0	
Cancer of pancreas	0	3	
Gastric cancer	0	3	
Malignant lymphoma	0	4	
Monoclonal gammopathy of unknown significance	0	3	
Immunoglobulin G_4 disease	0	1	
Hepatocellular carcinoma	0	1	
Gastrointestinal stromal tumor	0	2	
Cancer of esophagus	0	1	
Renal cell carcinoma	0	1	
Cancer of thyroid	0	1	
Malignant chondroma	0	1	

Level of CA 72-4 in those with and without malignancy at the time of recruitment in the raised CA 72-4 group

The baseline demographics of patients with and without malignancy in the CA 72-4 group are shown in Table 4. There was no significant difference in their baseline demographics (all p= NS).

There was also no significant difference in the median CA 72-4 level in those with and without malignancy in the CA 72-4 group [median (range) 9.3 (7.8-19.0) vs. 9.9 (7.8-17.8), respectively; p= 0.855] **[Table 4]**.

Table 4. Baseline demographics of patients with and without malignancy in the CA 72-4 group.

	CA 72-4 group		P-value
	Malignancy (n=7)	No malignancy (n=124)	
Age, years (range)	61.7 (39.7-68.2)	52.2 (26.1-75.3)	0.212
Sex; M: F	4:3	75: 49	0.860
Body mass index, kg/m^2 (range)	23.6 (18.2-27.4)	23.4 (17.6-41.4)	0.681
CA 72-4, U/ml (range)	9.3 (7.8-19.0)	9.9 (7.8-17.8)	0.855
Smoking:			0.115
Yes	2	12	
No	5	112	

At the end of 36 months follow-up

One hundred and twenty-four of the 131 patients in the CA 72-4 group and 682 of the 706 patients in the Control group without malignancy at the time of recruitment were followed-up prospectively for 36 months (94.7 % vs. 96.6 %, respectively; p= 0.279). All patients in both groups completed the 36 months follow-up.

No patients in the Control group [0 of the 682 patients (0 %)] were found to have a raised CA 72-4 on serial follow-up.

At the end of follow-up, no patients in either group were detected to have developed malignancy after further investigation [0/124 (0 %) in the CA 72-4 group vs. 0/682 (0 %) in the Control group, respectively; p= NS].

Serial CA 72-4 and development of malignancy in CA 72-4 group

Serial monitoring of the 124 patients in the CA 72-4 group without malignancy detected at the time of recruitment revealed two CA 72-4 patterns. One group of patients had a fluctuating CA 72-4 level with CA 72-4 fluctuating between normal and elevated levels [77 of the 124 patients (62.1%)] while another group had a persistently elevated CA 72-4 level [47 of the 124 patients (37.9 %)]. The graph showing the two patterns of CA 72-4 is shown in **Figure 1**.

There was no significant difference in the development of malignancy between the two types of serum CA 72-4 levels at the end of follow-up [0/77 (0 %) in those with fluctuating CA 72-4 level vs. 0/47 (0 %) in those with persistently elevated CA 72-4 level, respectively; p= NS].

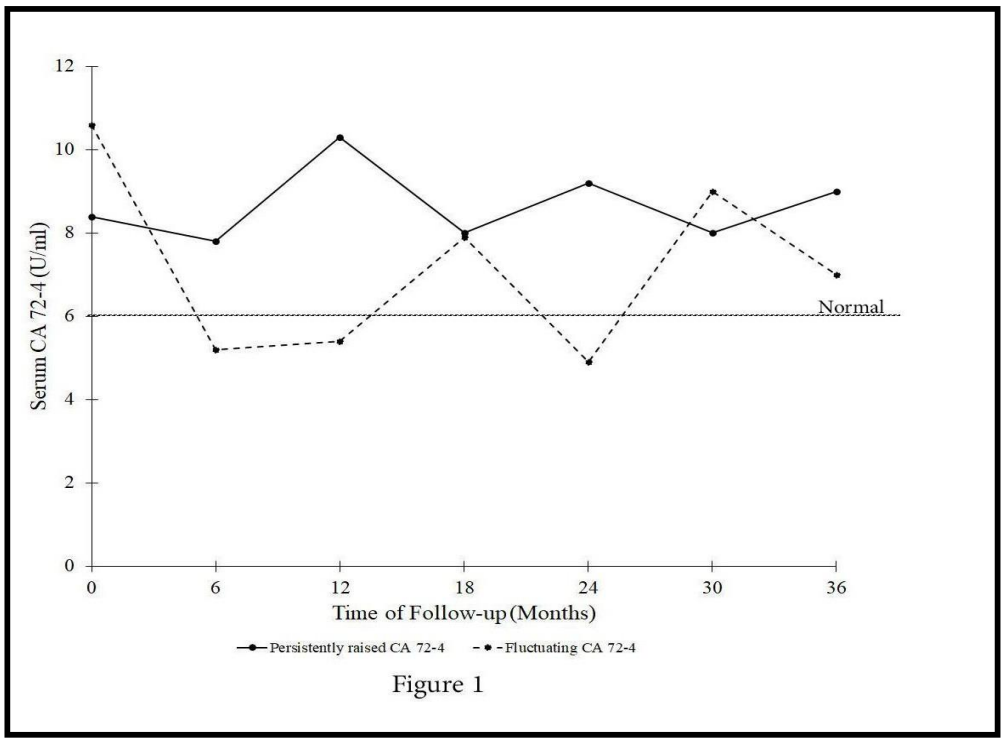

Figure 1. Graph showing the two patterns of serial CA 72-4 in the 124 patients in the CA 72-4 group without malignancy detected at the time of recruitment. (CA 72-4 level expressed as median) [Normal CA 72-4 < 6 U/ml].

Successful treatment of malignancy did not result in normalization of CA 72-4

All seven patients with malignancy in the CA 72-4 group successfully treated their underlying malignancy with remission demonstrated on assessment at 6 and 12 months, respectively.

The serial CA 72.4 in these seven patients diagnosed with a malignancy in the CA 72-4 group is shown in **Figure 2.** All seven patients (100 %) continued to have a fluctuating CA 72-4 level or a persistently raised CA 72-4 despite successful treatment of their underlying malignancy.

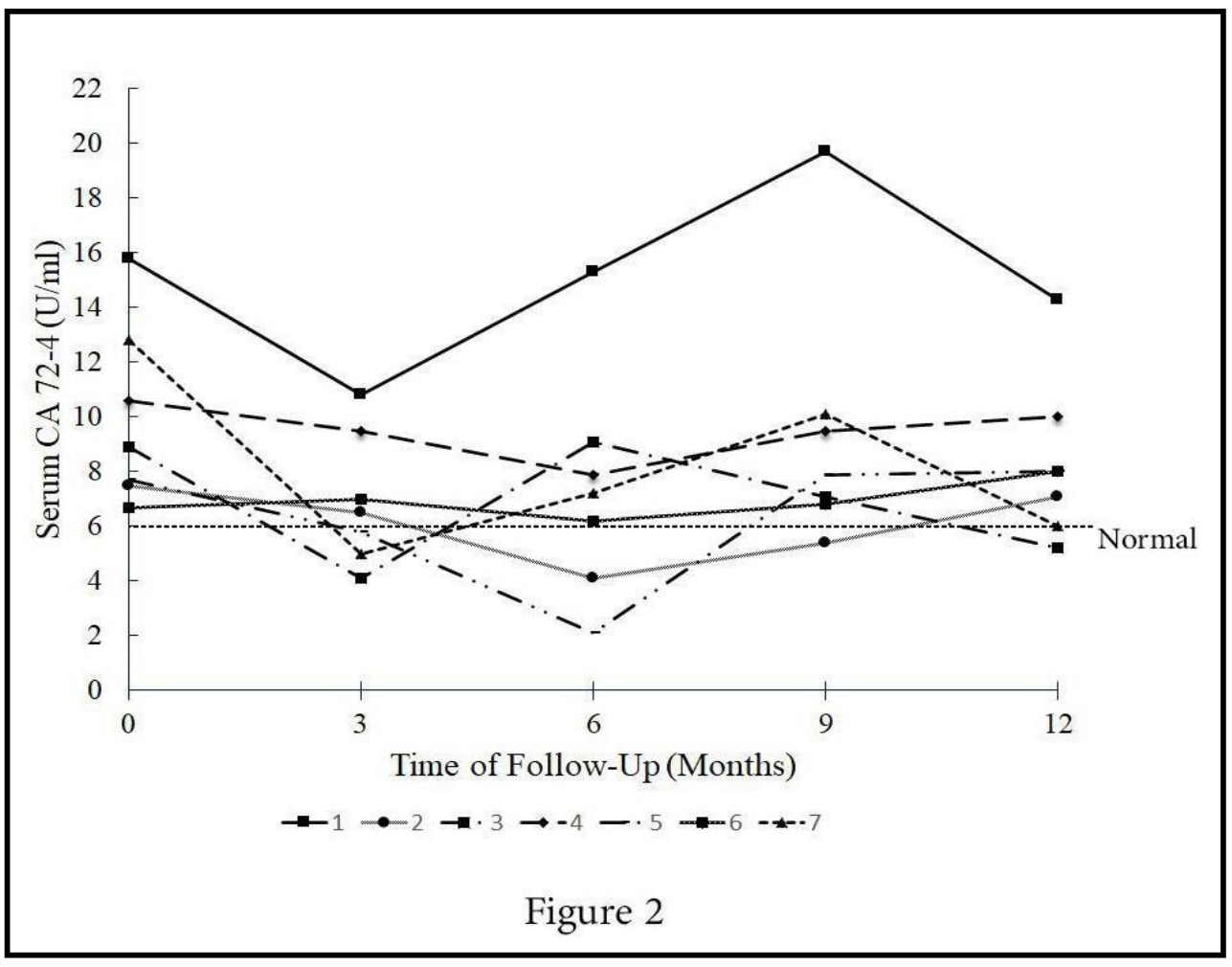

Figure 2. Graph showing the serial CA 72-4 level in the seven patients with malignancy in the CA 72-4 group (Normal CA 72-4 < 6 U/ml).

Discussion

This study showed that the prevalence of malignancy in an asymptomatic healthy population with raised CA 72-4 was low at only 5.3 %. The raised CA 72-4 was not due to gastric cancer, as none of those with raised CA 72-4 had gastric cancer on EGD. The malignancies were found in the lung (n=3), colon (n=2), endometrium (n=1), and breast (n=1), respectively.

We also demonstrated that an asymptomatic healthy population with a raised CA 72-4 was not associated with a higher risk of malignancy at the time of recruitment. So, it is even debatable if one even needs an EGD, much less further extensive investigation when the EGD was negative for gastric cancer.

Furthermore, the asymptomatic healthy population with raised CA 72-4 was not at a higher risk of developing malignancy on long-term follow-up. This shows that the value of following up with this particular group of asymptomatic healthy population is limited. When the initial thorough investigation for malignancy was negative, clinicians may be reassured that those with an incidentally raised CA 72-4 were not at a higher long-term risk of developing malignancy. In fact, no patients with a raised CA 72-4 developed malignancy at the end of follow-up.

However, patients with raised CA 72-4 were likelier to have a normal EGD. There was also a trend that the asymptomatic healthy population with grown CA 72-4 was less likely to have gastric intestinal metaplasia on EGD. This was unsurprising as all the patients with raised CA 72-4 were asymptomatic from a gastrointestinal point of view and only presented for routine health screening or health checks.

This study illustrated a few important points. CA 72-4 should not be routinely performed in asymptomatic people seeking routine physical health examinations. In fact, the raised CA 72-4 was not related to malignancy. Even in the seven patients found with malignancy at the time of recruitment, the expanded CA 72-4 was also unrelated to their underlying malignancy. This was because, as observed in all the seven patients in the CA 72-4 group with venom detected at the time of recruitment, none had normalization of CA 72-4 one year after successful treatment of their underlying malignancy. This meant that a certain proportion of healthy individuals in the general population may have a raised CA 72-4 level, like that observed with anti-nuclear antibodies.**[13]** So, clinicians should rely more on physical examination and sex- and age-related recommendations when deciding or selecting the correct type of tests or conditions to screen for in an asymptomatic healthy population presenting for health screening.

Even though there are fears that anti-nuclear antibodies may be present for many years before the onset of the first symptoms of connective tissue disease, **[14,15]** those with raised CA 72-4 levels did not seem to have a higher chance of developing malignancy on long-term follow-up. Considering that CA 72-4 may be presented in 7.2% of healthy individuals, **[3]** a raised CA 72-4 should not encourage serial monitoring of their level or serial extensive investigation for malignancy after the initial negative assessment.

Although CA 72-4 is useful for monitoring disease and prognosis in gastric cancer, **[16-18]** a raised CA 72-4 in a healthy population without any signs or symptoms does not warrant periodic extensive investigation for malignancy as it does not entail a higher risk of developing malignancy. A raised CA 72-4, unlike an expanded CA 19-9, **[19]**, was also not associated with a higher risk of developing malignancy on long-term follow-up. Therefore, having a raised CA 72-4 was not associated with a higher chance of malignancy at the time of recruitment or a higher chance of developing malignancy on long-term follow-up. Further investigation should only be performed when clinical symptoms occur or should only be performed based on age- and sex-related recommendations.

There were two patterns of CA 72-4. Most will have a CA 72-4 that fluctuates between normal and raised levels, while a smaller proportion will have a persistently raised CA 72-4 serially. However, neither of these two patterns was associated with a higher risk of developing malignancy at the end of 36 months of follow-up. The serial patterns of CA 72-4 also did not provide additional information on which way of raised CA 72-4 entailed a higher risk of developing malignancy or which subgroup of the asymptomatic healthy population with presented CA 72-4 should clinicians investigate for underlying malignancy. Therefore, serially monitoring the CA 72-4 pattern to select which patient to study for an underlying malignancy may not be a feasible clinical option.

Unfortunately, this study was unable to determine if the level of raised CA 72-4 would be a predictor for underlying malignancy as there was no significant difference in the median CA 72-4 between those with and without nastiness found at the time of recruitment in the CA 72-4 group. A larger scale study should be conducted to determine whether slight elevations above the upper limit of normal found in an asymptomatic healthy population is insignificant, and only marked hills above the upper limit of normal should raise the concern of malignancy like that reported with CA 19-9. **[20]**

There are a few limitations in this study. First, there was a selection bias as we only saw patients referred to a tertiary referral center. Secondly, the Ca 72-4 group was asymptomatic compared with the Control group as they only presented for routine health screening, introducing another bias into the study. Thirdly, the follow-up period was only 36 months. A longer follow-up may be needed to conclusively determine if having a persistently raised CA 72-4 or fluctuating CA 72-4 level may preclude a higher rate of developing malignancy when compared with those with normal CA 72-4. Finally, only 18FDG PET-CT was performed to assess for tumor recurrence or remission. We did not use a dual tracer PET-CT which should provide better detection for early recurrence of well-differentiated or well-to-moderately differentiated tumors, especially in tuberculous endemic areas. **[21-25]**

In summary, the prevalence of malignancy in an asymptomatic healthy population with raised CA 72-4 is low. An asymptomatic healthy population with expanded CA 72-4 also does not have a higher risk of malignancy at the time of recruitment or developing malignancy on long-term follow-up. Furthermore, considering the lack of association between malignancy and raised CA 72-4 in an asymptomatic healthy population, having a persistently raised or fluctuating CA 72-4 level without any signs or symptoms should not

be a reason for repeated extensive investigation to search for malignancy. However, it would be prudent to inform the patient that they should seek medical consult or consult their physician regarding clinical symptoms. It is worth keeping in mind that CA 72-4 can also be raised in a small percentage of the healthy general population who does not have malignancy and will not develop malignancy.

In conclusion, although CA 72-4 has a high specificity in those with gastric cancer, their occurrence is not synonymous with the presence of malignancy. The prevalence of malignancy in an asymptomatic healthy population with raised CA 72-4 is low at only 5.3 %. Asymptomatic healthy people with an expanded CA 72-4 are not at a higher chance of malignancy at the time of diagnosis, and they are also not associated with a higher risk of developing malignancy on long-term follow-up in asymptomatic healthy populations.

Abbreviations: CA 72-4- carbohydrate antigen 72-4; EGD- esophagogastroduodenoscopy; CT- computerized tomography; MRI- magnetic resonance imaging; PET-CT- positron emission tomography-computerized tomography

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The collection of data, editing of manuscript and data analyses were performed by K Hui.

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