

INCIDENCE OF CANCER IN PHYSICAL CHECKUP POPULATION WITH RISING OF SERUM CARCINOEMBRYONIC ANTIGEN

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Abstract

Carcinoembryonic antigen (CEA) is one of the tumor markers that use for screening colon cancers. However, the evidence-based of CEA in colorectal cancer screening is still not clear. A retrospective cohort study was designed to show incidence of cancer in physical checkup and screening serum CEA populations. Patients who attended physical checkup and screening serum CEA level at Suranaree University of Technology Hospital between January 2015 and January 2017 were enrolled and assigned into high and normal CEA level groups. Of total 310 enrolled participants, the mean plasma CEA levels in high and normal CEA level group were 7.44 and 1.84 ng/ml, respectively. After 12 months of observation, the high CEA level group provided a significance increased rate of cancer compared with a normal CEA group ($p=0.03$). Five cancers (3.2%) were detected in the high CEA level group at 11, 64, 114, 212 and 361 days and no cancer was detected in a normal CEA level group. In conclusion, patients who had undergone physical checkup and screening CEA, high CEA level patient provided an increased rate of cancer compared with normal CEA level patient.

Keywords: Carcinoembryonic antigen, CEA, tumor marker, cancer screening

Introduction

Carcinoembryonic antigen (CEA) is an oncofetal antigen, which is present in fetus and patient with malignancies especially in epithelial cancer. Actually, it can normally present within low concentrations in adults (Gold and Freedman, 1965; Thomson *et al.*, 1969; Fletcher, 1986; Summary of an NIH Consensus Statement, 1981; Duffy *et al.*, 2003). In current practice, many hospital use CEA in a part of program screening of colon

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cancer. However, there is lack of a data to use CEA in screening colorectal cancer. In prior studies, there were data that show correlation of CEA level and colon cancer and they found a high CEA level had 30-40% of sensitivity and 87% of specificity to detect colon cancer in Duke' A and B stage (Duffy *et al.*, 2003; Locker *et al.*, 2006; Ransohoff and Sox, 2016; Lin *et al.*, 2016). Additionally, they found 40-57.48% of high CEA patient with gastrointestinal symptoms had gastrointestinal malignancies and CEA level was a prognostic factor of patient with colon cancer (Hine *et al.*, 1978; Arnaud *et al.*, 1980; Carriquiry *et al.*, 1999). Moreover, the high CEA level can be found in benign condition such as smoker population, chronic lung disease, ulcer or inflammation of gastrointestinal tract and liver and renal compromised (Fletcher, 1986; Duffy, 2001).

From the current data, fecal occult blood test, flexible sigmoidoscopy, double-contrast barium enema, computed tomography colonography, and colonoscopy are only recommended to use in colorectal cancer screening (Locker *et al.*, 2006, Provenzale *et al.*, 2015; US Preventive Services Task Force *et al.*, 2016).

Therefore, we conducted a retrospective cohort study to show incidence of cancer in physical checkup and screening serum CEA populations.

Materials and Methods

Patients

We enrolled patients who receiving physical checkup and screening serum CEA level at Suranaree University of Technology Hospital between January 2015 and January 2017. All patients were older than 18 years old. We excluded patients with conditions confounding serum CEA level, including history of ulcer or inflammation of the gastrointestinal tract, deterioration of the renal and hepatic function, and history of cancer. All participants provided written informed consent. The study has been approved by the committee Institution Review Board of Suranaree University of Technology.

Data Collection

All participant information was collected such as sex, age, weight, height, history of smoking and alcohol drinking, and CEA level. Participants were assigned to high and normal CEA level groups. The definition of the high CEA level was above 5 nanogram per millilitre. All participants were observing 12 months for detecting cancer.

Outcomes

The primary endpoint was the incidence of cancer in high CEA level group compared with a normal CEA level group. The secondary endpoints were factors which influential to cancer occurrence in physical checkup participants.

Statistical Analysis

The study population was calculated by W.G. cochrane (1953). The incidence of cancer derived from prior study (Hine *et al.*, 1978). The study required 377 participants to provide a power of 80% and a two-sided significance level of 0.05. Incidence of cancer between high and normal CEA level group were compared by Fisher's exact test. Finally, the multivariate analysis of the possible factors influential to cancer occurrence was performed.

All statistical analyses were performed using SPSS version 16.0 for Windows software (SPSS Inc., Chicago, IL) and P values below 0.05 were considered statistically significant.

Results

Between January 2015 and January 2017, there were 24,945 participants receiving physical checkup and screening serum CEA level at Suranaree University of Technology Hospital and 243 participants had a high CEA level (9.74%). 155 eligible participants were recruited in both high and normal CEA level groups. The mean age was 55.38 years and male was predominant (76.8%). The mean BMI was 28.16 kg/m². Smoking and alcohol drinking status were significant higher in high CEA level group. The mean CEA levels was 7.44 and 1.84 ng/ml in high CEA level group and normal CEA level

group, respectively. The baseline characteristics were shown in Table 1.

After 12 months of observation, cancers were detected in five participants (3.2%) in the high CEA level group and no cancer was detected in normal CEA level group. In five cancer participants, two were colorectal cancer, one was breast cancer, one was prostate cancer, and one was oral cancer. Incidence of cancer was significantly higher in the high CEA level group, $p=0.03$. (Table 2)

According to the two colon cancer participants, the age at time of diagnosis were 80 and 52-year-old, no complaint about gastrointestinal symptom and negative physical examination in the date of physical checkup in both participants, the cancer was detected by colonoscopy due to ages more than 50 with average risk, both of cancer were stage IIIB, and undergone surgery with adjuvant chemotherapy. In breast cancer participant, the

age at time of diagnosis was 47-year-old, the cancer was detected by physical examination in the date of physical checkup, the cancer was stage IIIA, and undergone surgery with adjuvant chemotherapy, radiation, and antihormonal therapy. In prostate cancer participant, the age at time of diagnosis was 56-year-old, the cancer was detected by rising of prostate-specific antigen with no complaint about genitourinary symptom and negative physical examination, participant was referred to urologist for biopsy, the cancer was stage IVB, and undergone medical castration with antiandrogen therapy. Finally, in oral cancer participant, the age at time of diagnosis was 83-year-old, the cancer was detected by revealed oral ulcer mass with cervical lymphadenopathy while physical examination several months after the date of physical checkup, the cancer was at least clinical stage III, and refer to otolaryngologists for treatment.

Table 1. Baseline patient characteristics

	High CEA level group (n=155)	Normal CEA level group (n=155)	Total (n=310)
Age (years)	55.92±11.66	54.85±10.20	55.38±10.95
Sex - Male	122 (78.7%)	116 (74.8%)	238 (76.8%)
- Female	33 (21.3%)	39 (25.2%)	72 (23.2%)
Weight (kg)	66.16±13.94	68.31±13.50	67.24±13.74
Height (cm)	164.34±15.26	164.95±7.97	164.64±12.16
BMI (kg/m ²)	31.32±87.40	25.00±3.86	28.16±61.84
Smoking status*			
- Current smoking	40 (25.8%)	10 (6.5%)	50 (16.1%)
- Past smoking	8 (5.2%)	40 (25.8%)	48 (15.5%)
- Never smoking	100 (64.5%)	100 (64.5%)	200 (64.5%)
- Unknown	7 (4.5%)	5 (3.2%)	12 (3.9%)
Alcohol drinking status*			
- Current drinking	60 (38.7%)	54 (34.8%)	114 (36.8%)
- Past drinking	1 (0.6%)	18 (11.6%)	19 (6.1%)
- Never drinking	87 (56.1%)	81 (52.3%)	168 (54.2%)
- Unknown	7 (4.5%)	2 (1.3%)	9 (2.9%)
CEA level (ng/ml)*	7.44±3.31	1.84±1.04	4.64±3.72

* Significant difference ($p<0.05$)

Table 2. Incidence of cancer in 12 months

	High CEA level group (n=155)	Normal CEA level group (n=155)
Incidence of cancer in 12 months*	5 [#] (3.2%)	0

* Incidence of cancer was significantly higher in high CEA level group, $p=0.03$ by Fisher's exact test.

[#] Two were colorectal cancer, one was breast cancer, one was prostate cancer, and one was oral cancer.

The duration of cancer diagnosis after receiving physical checkup and screening serum CEA level in five participants were 11 to 361 days, respectively. There is one cancer participant death due to oral cancer in 193 days after cancer diagnosis and 554 days after receiving physical checkup and screening serum CEA level. (Table 3)

In the medical record data at Suranaree University of Technology Hospital, there were 29 participants (18.7%) in the high CEA level group undergone colonoscopy with no compliant any gastrointestinal symptom. The most common indication for colonoscopy was the ages more than 50 with average risk in 21 participants (72.4%) however there were 8 participants (27.6%) undergone colonoscopy due to only a reason of high CEA level. The result of colonoscopy were normal in 11 participants (37.9%) and abnormal in 18 participants (62.1%) The colon cancer was found in two participants (6.9%) (Table 4). Unfortunately, there were no available medical record of participants who undergone to do other investigation beside colonoscopy.

According to multivariate analysis, there were no significant of gender, age, body weight, height, body mass index, smoking

history and alcohol drinking history in the incidence of cancer (all factors $p > 0.05$).

Discussion

In this study, 3.2% of participants who had a high serum CEA level were diagnosed cancer at 12 months. The most common of cancer that found in this group was early stage colon cancer and diagnosed via colonoscopy.

The incidence of cancer in this study was lower than prior study. In prior study, there reported incidence of cancer up to 57.38% in abnormal CEA level (Hine *et al.*, 1978). However, the participants in that study had an abnormal symptom before enrollment, which contrast to our study that enrollment only healthy participants.

Despite this study found a higher incidence of cancer in high serum CEA level participants, there were no current guideline recommendation to management patient who had high CEA level. Thus, some of participants undergone colonoscopy with a standard indication with is the ages more than 50 with average risk.

Table 3. Data of five cancer participants

No.	Cancer type	Age (year-old)	Staging [#]	Cancer detection (days)	Treatment	Status
1	Colon	80	IIIB	11	Right half colectomy and CMT	Alive
2	Breast	47	IIIA	64	Right MRM and CMT, RT, antihormonal therapy	Alive
3	Colon	52	IIIB	114	Sigmoidoscopy and CMT	Alive
4	Prostate	56	IVB	212	Medical castration and antiandrogen therapy	Alive
5	Oral	83	At least III	361	Unavailable [§]	Dead*

MRM is Modified Radical Mastectomy, CMT is chemotherapy, and RT is Radiation

* Participant who diagnosed with oral cancer dead at 193 days after cancer diagnosis and 554 days after receiving physical checkup and screening serum CEA level.

[#] Staging by AJCC Cancer Staging Manual, Eighth Edition

[§] This patient was referred to another hospital and there was no data of medical record.

Table 4. Colonoscopic finding in 29 high CEA level participants

Colonoscopic finding	n (%)
Benign polyp	13 (44.8%)
Normal finding	11 (37.9%)
Colitis	3 (10.3%)
Colon cancer	2 (6.9%)

According to five cancer participants, the colon cancer was detected by colonoscopy and the prostate cancer was detected by the Prostate-Specific Antigen test however the breast and oral cancer were detected by physical examination. Thus, comprehensive history taking and physical examination was the key point for management of these population and guided to choose proper further investigation.

According to low sensitivity and specificity of the CEA levels in early stage of colorectal cancer, the CEA levels might not be the good choice for using in colorectal cancer screening and patient with abnormal result may undergone colonoscopy without appropriate indication might associate with the potential for colonoscopy-associated complications. Thus, expert panel of the American Society of Clinical Oncology not recommended to use the serum CEA as a screening or diagnostic test for the colorectal cancer (Locker *et al.*, 2006). However, the CEA levels had a benefit for the follow-up of patients with diagnosed colorectal cancer (Locker *et al.*, 2006). In the current guideline for colorectal cancer screening (Lopes *et al.*, 2019), for people who were asymptomatic, were ages 50 to 75 years, had no family history of colorectal cancer, were at average risk, and were in settings with high incidences of colorectal cancer, the following screening options were recommended: guaiac fecal occult blood test and fecal immunochemical testing, flexible sigmoidoscopy, and colonoscopy.

According to the improvement of technologies for sequencing DNA, testing of serum so-called liquid biopsy to find the tumor DNA was possible. The Next-generation sequencing was a type of DNA sequencing technology that uses parallel sequencing of multiple small fragments of DNA to determine sequence and development of methods based on this technology can analysis cell free DNA (cfDNA) in plasma which provided the opportunity for a new diagnostic approaches (Haber and Velculescu, 2014, Neumann *et al.*, 2018). In the cancer screening aspect, there had few studies that developed this method to help in screening and diagnosis of the cancer. One was the study which used cfDNA for

examine plasma from healthy individuals however the result show no solid tumor-derived alterations in driver genes were identified in plasma of the healthy individuals. But the result in patients with stage I or II of colorectal, breast, lung, and ovarian cancer, this method could detect somatic mutations in 71%, 59%, 59%, and 68%, respectively (Phallen *et al.*, 2017). In another study which applied the test called CancerSEEK and they test in patients with nonmetastatic cancers and found 69-89% in sensitivity and greater than 99% in specificity (Cohen *et al.*, 2018). Unfortunately, The American Society of Clinical Oncology and the College of American Pathologists were not recommended to use the cfDNA as a screening test for the cancer outside of a clinical trial due to lack of current evidence of clinical validity and clinical utility. But some ctDNA assays had demonstrated clinical validity and utility with certain types of advanced cancer for predictive of response to targeted treatment such as EGFR mutation in non-small cell lung cancer and KRAS genotyping in colorectal cancer (Merker *et al.*, 2018).

The limitation of this study was smaller sample size than expected due to loss contact in some participants and duration of 12 months for cancer detection may not sufficiency and there was no available medical record of some participants who undergone to do investigation and treatment in other hospital or do other investigation beside colonoscopy. Therefore, desirable future studies should be sufficiently powered, use longer duration to follow up participants, and find proper management for asymptomatic high CEA level population. Finally, the development of cfDNA technologies might provide the opportunity for a new method to detect the early stage cancers which might improve the result of treatment of cancer patient.

Conclusions

Among patients who had undergone physical checkup and found high serum CEA level have higher incidence of cancer at 12 months.

Conflicts of Interest

The author declare that there are no conflicts of interest regarding the publication of this article.

Acknowledgments

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