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BIOMARKERS FOR CANCER RISK AMONG PEOPLE ATTENDING A COMMUNITY EVENT: AN OBSERVATIONAL COHORT STUDY IN JOHOR, MALAYSIA

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ABSTRACT

Introduction: Cancer is the second most common cause of death in Malaysia. Early detection and treatment may help to optimise outcomes, but most cancer patients in Malaysia present with late-stage disease. The aim of this community health project was to improve community awareness of the risks of cancer (among other non-communicable diseases), and the benefits of screening for disease prevention and early detection. **Methods:** Community health screening was conducted during the 2016 Kembara Mahkotacommunity event in Johor, Malaysia. Blood-based biomarkers were used to screen for risk of cardiovascular disease, diabetes, cancer and thyroid disease in the population attending the event. Cancer screening involved measurement of carcinoembryonic antigen (CEA), a marker of colorectal cancer risk, cancer antigen 125 (CA125) for assessment of ovarian cancer risk, prothrombin induced by vitamin K absence II (PIVKA II) levels for hepatocellular carcinoma (HCC) risk, and pepsinogen I/II (PG I/II) ratio for assessment of gastric cancer risk. Individuals identified as high risk were referred for specialist follow-up. **Results:** A total of 2744 individuals participated in biomarker screening.CEA and CA 125 levels indicated that 4–7% of the population had high cancer risk. HCC risk was high in 17% of individuals, based on PIVKA II levels, and 3% were at risk of gastric cancer based on the PG I/II ratio. **Conclusion:** Community health projects such as ours are required to raise awareness of the risks of common preventable diseases, and to encourage individuals to participate in health checks and disease screening programmes.

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INTRODUCTION

Cancer is a leading cause of morbidity and mortality in Malaysia, accounting for 15% of total deaths in 2012.[1]Although the age-standardised incidence of cancer has been gradually decreasing in Malaysia over recent years, the number of cancer deaths per year is increasing,[2] presumably because of changing demographics and an increasing number of older people. More than 100,000 new cancers were diagnosed in Malaysia between 2007 and 2011, the most common being breast cancer, colorectal cancer, cancer of the trachea/bronchus/lung, lymphoma and nasopharyngeal cancer.[2]

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Prevention and early detection of cancer can reduce the burden of disease management for individuals and society, but Malaysians often present with late-stage disease.[2] This is because many cancers do not cause symptoms or appear as detectable tumours until they have progressed to a relatively advanced stage. Cancer screening has the potential to identify cancers at an early stage,[3] when they are easier to treat, and may reduce cancer-related mortality.[4] However, many screening programs involve imaging studies such as mammography or colonoscopy, which can be time-consuming and costly, or procedures that patients are often reluctant to undertake, such as cervical smears.[5,6] Therefore, the ease of cancer screening would be greatly enhanced by biomarkers that can be detect early cancer in an easily obtained body fluid sample, like blood or urine.[7] To obtain clear local non-communicable disease (NCD) risk data in the general population of Johor, Malaysia, we conducted a community-based project in which members of public were encouraged to undergo blood-based

biomarker tests to screen for various NCDs, including cancer. The aim of this project was to improve community awareness of the risks of these common NCDs, and the benefits of screening for disease prevention and early detection. Here we report the results of the cancer screening arm of the project, in whichblood levels of various cancer biomarkers were measured to assess risk of colorectal cancer, ovarian cancer, gastric cancer and hepatocellular carcinoma (HCC). Results of screening for other NCDs (type 2 diabetes, cardiovascular disease and thyroid disease) will be reported separately.

MATERIALS AND METHODS

Study population: Community health screening was conducted during the Kembara Mahkota event, which took place from the 14th to the 17th of May 2016. The Kembara Mahkota is a royal "meet the people" tour that coversthe 10 districts of the state of Johor. During the Kembara Mahkota event, members of the Johorian public aged ≥18 years were offered free blood-based biomarker tests to screen for risk of CVD, type 2 diabetes, cancer and thyroid disease. A total of 2744 individuals participated in biomarker screening. They were briefed by district healthcare personnel, and asked basic questions regarding their medical, surgical and family disease history. Based on self-declaration, all volunteers were free from active or past history of cancer. Collected blood samples were transported to Johor Specialist Hospital for analysis. This study was approved by the Johor State Health Department. All participants gave informed consent.

Biomarker assay methods: Cancer screening involved measurement of carcinoembryonic antigen (CEA), a marker of colorectal cancer risk, cancer antigen 125 (CA125) for assessment of ovarian cancer risk, prothrombin induced by vitamin K absence II (PIVKA II) levels for HCC risk, and pepsinogen I/II (PG I/II) ratio for assessment of gastric cancer risk. Blood sample analyses were performed daily at Johor Specialist Hospital. All analyses were performed on the Abbott ARCHITECT system.

Biomarker levels and disease risk: Biomarker cut-off levels interpreted as being indicative of high risk of disease were based on Abbott biomarker assay sensitivities and evidence-based reference values. In general, elevated cancer risk was defined as CEA>5.0 ng/mLor CA125 >35U/mL.[8,9] PIVKA II >40 mAU/mLindicated increased risk of HCC,[10] and PG I/II ratio <3.0 indicated increased risk of gastric cancer.[11]

Follow-up and education: When test results indicated high risk of disease, the individuals were informed that their results were ready for collection from the health centres in their respective districts and referred to specialist physicians for follow-up. Brief lectures on cancer, diabetes, heart disease and hypertension were given for the benefit of all visitors of the healthcare booth, irrespective of whether or not they decided to participate in biomarker disease screening.

RESULTS

Subject characteristics: Individuals who took part in biomarker screening (n=2744) were aged between 18 and >80 years old.50.6% of participants were female. 93% of participants were <60 years old. All participants declared that they did not have active nor history of cancer.

Cancer biomarkers: The prevalence of biomarker levels indicating cancer risk are shown in Figure 1. A CEA level >5.0 ng/mL or a CA125 level >35 U/mL indicated a high risk of cancer in 7.4% and 4.3% of the population, respectively. Risk of HCC was high in 16.6% of the population (PIVKA II >40 mAU/mL), and 2.6% of individuals had a high risk of gastric cancer (PG I/II ratio <3). Across the whole group, CEA levels ranged from 0.5 to 68.4 ng/mL, and there was a trend towards increasing levels with age (Table I and Figure 2). The range of CA 125 levels was from 1.6 to 493.1 U/mL and there was no apparent trend with age (Table I). PIVKA II levels varied from 1 to 30,003 mAU/mL, but the median level was around 30 to 34 mAU/mL in all age groups (Table I and Figure 2). The median PG I/II ratio was around 7 in all age groups, but the individual level varied from 0 to 24.0 across the population (Table I and Figure 2). There was no apparent difference in cancer biomarker levels between the men and women in this population (Table I and Figure 3).

DISCUSSION

The Kembara Mahkohta event, which is traditionally well attended by a large cross-section of the community, provided an opportunity to identify individuals at high risk of CVD, type 2 diabetes, cancer and thyroid disease, and to improve awareness of these common NCDs within the general Johor population. Information offered to people visiting our healthcare booth was aimed at improving awareness of disease and the importance of screening for early detection or prevention of disease. Consequently, 2744 individuals accepted our offer of blood-based biomarker testing to assess their disease risk. Individuals identified as being at high risk were referred for specialist follow-up, thereby allowing them to begin appropriate therapy and/or adopt lifestyle and dietary changes that could improve long-term outcomes. Based on data for new cancers diagnosed between 2007 and 2011, HCC, colorectal, gastric and ovarian cancers rank amongst the ten most common cancers in Malaysia,[2,12]but are generally detected at a late stage.[2] Early detection of these cancers is important because, if diagnosed early, when patients have a relatively good prognosis, effective treatment can be administered, and survival improved.[13-18] Levels of CEA and CA125 may be elevated in colorectal and ovarian cancers, respectively, as well as a variety of other malignancies and non-malignant conditions.[8,9] Unfortunately, CEA and CA125 assay sensitivities do not reliably detect early-stage colorectal or ovarian disease.[8,9,15,19]The current recommendation for Asia Pacific is to screen for colorectal cancer using a faecal occult blood test among individuals aged between 50 and 75 years.[20] However, many Malaysians are reluctant to take this test because they find it embarrassing, uncomfortable and time consuming.[21] Nevertheless, based on levels of CEA and CA125 in our study population, approximately 4–7% of individuals had biomarker levels indicative of colorectal cancer or ovarian cancer risk, and were referred for further clinical evaluation. PIVKA-II and PG I/II ratio have potential as biomarkers for the early diagnosis of HCC and gastric cancer, respectively.[10,11]PIVKA-II is an abnormal prothrombin protein that is elevated in HCC,[10]andcirculating pepsinogens indicate atrophic gastritis and other early gastric lesions, with a nonlinear continuous association between PGI/II ratio and risk of gastric cancer.[11]In our study, PIVKA-II indicated that a relatively high proportion of the population (17%) was at risk of HCC, therebyreinforcing the importance of considering a screening programme to identify early-stage HCC in the Malaysian population.[22] The PG I/II ratio indicated that only 3% of the population were at increased risk of gastric cancer, supporting the suggestion that screening for gastric cancer in asymptomatic individuals in Malaysia may not be practical or cost-effective.[14]All individuals identified as being at risk of HCC or gastric cancer were referred for further diagnostic procedures, such as appropriate imaging and endoscopy. Previous research has identified a number of barriers to cancer screening among people in Malaysia.[5,21,23-26] These include a low awareness of cancer screening, a lack of information from physicians about cancer screening, poor perception of the effectiveness of screening to detect cancer, financial constraints, long waiting lists, and spiritual/religious fatalism about developing cancer ("God's will).[5] Some of this research identifies a lack of "cues to action" in Malaysia, to stimulate individuals to access cancer screening.[5] This may involve community-wide education about cancer screening (e.g. through mass media campaigns),[5] or greater encouragement/endorsement for cancer screening from primary care physicians.[26,27] In a multicultural country like Malaysia it is also important that information on cancer screening is available in a range of languages.[5] It is also important for physicians to understand the cultural and religious context in which patients seek health care, because patients' beliefs are key in determining their participation in screening programs.[28] A key concern in cancer screening is the potential impact on patients of a false positive result, both in terms of

physical and psychological harm.[3,27,29] Therefore, it is essential that cancer biomarkers have been shown to have high sensitivity and specificity, to maximise benefit and minimise harm.[30]

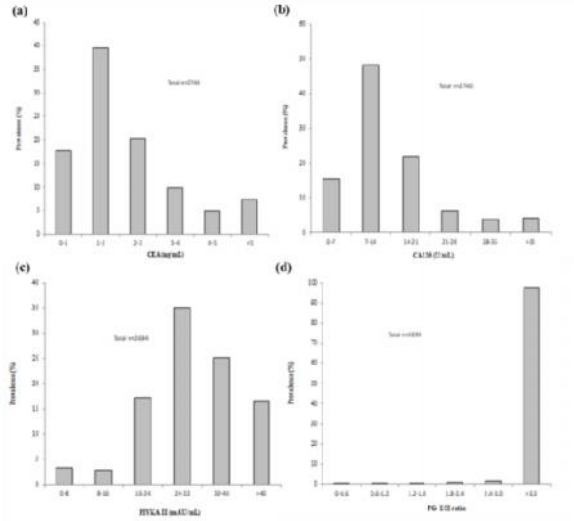

Figure 1. Distribution of cancer biomarkers within the population screened: (a) CEA, carcinoembryonic antigen; (b) CA 125, cancer antigen 125; (c) PIVKA II, Prothrombin induced by vitamin K absence II; (d) PG I/II ratio, ratio of pepsinogen I/II

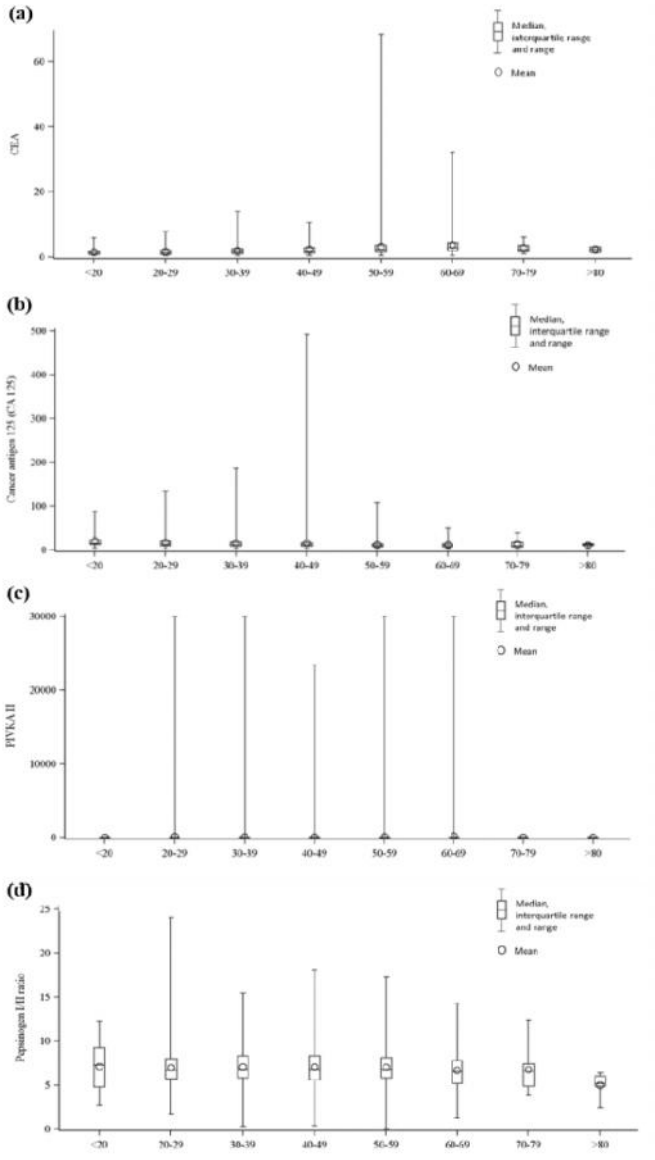

Figure 2. Levels of cancer biomarkers in different age groups: (a) CEA (ng/mL); (b) CA 125 (U/mL); (c) PIVKA II (mAU/mL); (d) PG I/II ratio

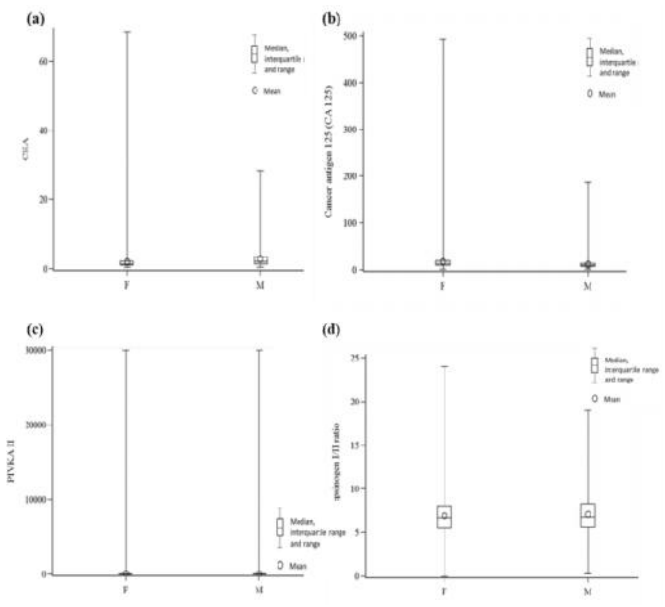

Figure 3. Cancer biomarker levels in men and women: (a) CEA (ng/mL); (b) CA 125 (U/mL); (c) PIVKA II (mAU/mL); (d) PG I/II ratio. F: Female; M: Male

The predictive properties of CA125 and CEA are relatively well defined. CA125 has a positive predictive value (PPV) of 58% for ovarian cancer, a negative predictive value (NPV) of 92%, and a diagnostic odds ratio of 21.2, indicating good test performance.[31] The PPV and NPV of CEA for colorectal cancer are 89.97% and 71.1%, respectively, with a diagnostic odds ratio of 7.9, indicating lower test performance than for CA125.[31] At the threshold we used (40 mAU/mL), PIVKA II has a high specificity (81 to 98%), so is unlikely to associated with a high rate of false positives.[32]

However, the sensitivity of PIVKA II is between 48% and 62%,[32] although the predictive value of PIVKA II for HCC is enhanced when combined with another liver cancer biomarker – alpha-fetoprotein (AFP).[10] A pepsinogen I/II ratio of <3.0 has been shown to have a sensitivity of 84.6% and a specificity of 67.2% when used alone for gastric cancer screening, but the specificity is enhanced if this biomarker is combined with a pepsinogen I level of <70 mg/mL.[33] A meta-analysis of different thresholds for pepsinogen screening found that this combination of biomarker values (pepsinogen I <70 mg/mL and PGI/II ratio of <3.0) had the best performance properties for screening, although the false positive rate was still relatively high at 28.6%.[34]

This community-based study was conducted in conjunction with the Kembara Mahkotaevent that allowed the screening of individuals across the 10 districts of Johor. Nonetheless, the sampling method in this study is limited to the attendees of the event from the 10 districts of Johor. Further, cancer risk profiling of the individuals based on their family history of cancer was not available.

In conclusion, to effectively implement strategies to reduce the incidence and improve the prognosis of common and preventable NCDs, including cancer,community health projects such as ours are required to raise disease awareness and encourage individuals to participate in health checks and disease screening programmes. Future studies directed specifically at population cancer screening using serum biomarkers may wish to use a combination of biomarkers to enhance the predictive properties of screening. Further follow-up is required to determine the nature of interventions and outcomes in the high-risk patients identified and referred for specialist follow-up in our population-based study.

Table 1.

Participant subgroups	CEA, ng/mL		CA 125, U/mL		PIVKA II, mAU/mL		PGI/II ratio	
	Mean	Median (Range)	Mean	Median (Range)	Mean	Median (Range)	Mean	Median (Range)
Gender								
Females	2.04	1.5 (0.5–68.4)	17.67	13.5 (1.9–493.1)	105.28	28 (0–30,003)	6.94	6.7 (0–24.0)
Males	2.84	2.2 (0.5–28.5)	11.77	10 (1.6–187.1)	59.71	34 (1–30,003)	7.09	6.8 (0.3–19.0)
Age groups								
<20 years	1.60	1.4 (0.5–6.0)	20.80	15.05 (4.6–87.6)	29.81	31 (3–60)	7.09	7.3 (2.7–12.3)
20–29 years	1.70	1.4 (0.5–7.9)	17.32	13.00 (1.6–135.3)	92.71	30 (1–30,003)	6.99	6.7 (1.7–24.0)
30–39 years	1.98	1.6 (0.5–14.1)	15.99	12.50 (2.5–187.1)	74.85	31 (1–30,003)	7.07	6.8 (0.3–15.5)
40–49 years	2.33	1.8 (0.5–10.6)	15.73	11.80 (2.1–493.1)	69.31	31 (0–23,389)	7.05	6.8 (0.4–18.1)
50–59 years	3.13	2.3 (0.5–68.4)	12.12	10.5 (1.9–108.2)	78.79	30 (2–30,003)	7.02	6.8 (0–17.3)
60–69 years	3.63	2.9 (0.5–32.2)	11.92	10.4 (2.7–51.2)	184.36	31.5 (1–30,003)	6.68	6.5 (1.3–14.3)
70–79 years	2.77	2.3 (1.1–6.2)	14.38	8.9 (3.3–39.1)	30.19	30 (21–40)	6.74	6.6 (3.9–12.4)
>80 years	2.30	2.3 (1.3–3.3)	11.14	12.3 (4.4–15.1)	29.80	34 (15–41)	5.00	5.2 (2.5–6.4)

CEA, carcinoembryonic antigen; CA 125, cancer antigen 125; PIVKA II, prothrombin induced by vitamin K absence II; PG, pepsinogen.

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