Risk Factors for A Five-Year Death in The InterASIA-South Cohort

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Objective: *To determine the mortality rate and risk factors for death in a selected population in Songkhla province in southern Thailand.*
Material and Method: *The southern subjects were part of the Thai cohort which together with the cohort from China comprised the InterASIA survey which was conducted in the year 2000. Collected variables were the conventional ones and included the 2 ethnic groups which are specific for southern Thailand, i.e. Malay Muslims and Thai-Chinese Buddhists. Causes of death were determined by reviewing hospital records, verbal autopsies and a consensus by 2-3 physicians. Kaplan Meier's model was used to evaluate the independent factors related to death.*
Results: *The follow-up was 5 years. Out of the original 1,006 subjects, the status could be examined in 86% and of these, 50 had died giving the Kaplan Meier 5-year survival rate of 94.3%. Sixteen died from cardiovascular diseases (CVD), 6 from strokes and 10 from coronary heart disease, and 15 died from cancer. Half of the deaths occurred in subjects older than 70 years. Independent risks for death were age, hypertension and diabetes mellitus. Risk for the major causes of death did not include ethnicity. Similar to the only existing prospective report of risk factors for death in Thailand (the Electricity Generating Authority of Thailand study), neither high total cholesterol, high triglyceride nor obesity were independent risks for death from CVD, but the present study differed in that the high density lipoprotein cholesterol was not found to be a protective factor for CVD death.*
Conclusion: *Risk factors for death in a five-year follow-up in Southern Thailand did not include lipids, ethnicity or urbanization but hypertension and diabetes mellitus did.*

Keywords: *CVD, cancer, South Thailand, ethnicity*

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Cardiovascular disease (CVD) is a health burden world wide and it has become more prominent in the developing countries following "improved" socioeconomic factors and the widespread adoption of a "Westernized" life style[1-9]. However, the risk factors for CVD in developed and less well developed countries may differ in both magnitude and specificity. Lacking adequate data of incidences in developing countries, one can only refer to studies on the application of the Framingham risk function (for predicting coronary artery disease) to appreciate the differences in risks among races and geographical regions[10-12]. These reports showed that the risk factors were similar but the magnitude of some of the factors and of the events can be different among the population groups such as the non-Caucasian American, certain European groups and the Chinese[11,12]. For example, the Chinese cohort had less proportion of high total cholesterol (TC) and hypertension (HT), similar prevalence of diabetes mellitus (DM) but more of the males smoked[11].

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A report from Singapore suggested that differences in risks among the ethnic groups were no longer found once the evaluation was made only among those with DM[13]. For Thailand, a cohort from the Electricity Generating Authority of Thailand (EGAT) study was followed for 12 and 17 years[14,15], and it was found that conventional risks (e.g. diabetes, hypertension, age etc.) for CVD mortality were similar to other reports[10,12] except TC and triglyceride (TG) were not found to be independent factors despite 50% of the subjects having TC > 225 mg/dl or TG > 160 mg/dl (approximated from the published average TC of 5.8 mmol/l and TG of 1.8 mmol/l). However, the present cohort was well-off economically, had easy access to health care and lived mainly in the metropolitan area. In 2000, a cross-sectional evaluation of risks for CVD was made in Thailand and mainland China (InterASIA)[16,17]. One of the Thai components was from Songkhla province representing the Southern region. These subjects were followed for 5 years thus allowing an evaluation of factors related to death.

Material and Method

The details of the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA) had been reported[16,17]. In Thailand, the survey was conducted from May to October 2000 and the details of the survey in Songkhla province are reported together with the present study[18]. In brief, the survey involved individuals aged 35 years and over, randomly sampled and stratified according to age group, gender and district, whether rural or urban. Interviews regarding basic socio-demographic variables included household income and ethnicity, whether Muslims of Malay extraction or Buddhists of Thai/Chinese extraction[18]. Smoking was recorded. The conventional physical examination included the measurements of blood pressure, body weight, height, waist and hip circumferences. Fasting venous blood samples were taken for lipid and glucose.

The sampling districts in Songkhla province were Klang-Na, Hat Yai city (non-slum urban); Kow-Seng, Songkhla city (slum urban); Klong-Hoi-Khong (developed rural); and Rhattapoom (developing rural). The total subjects numbered 1,006. All subjects were re-contacted by letter, telephone or in person for re-examination. Those who had died, moved or lost were identified. Those moved out of the district were determined from interviewing neighbors or interrogating social registrations but their alive/dead status could not be traced.

The likely cause of death was determined through interviews with close relatives by trained health personnel and if possible by 2 of the authors (PT, TY). All related hospital records where the deceased had attended (i.e. not only the last attendance whose outcome resulted in death) were examined. Cause of death was agreed by the two physicians and in case of uncertainty, arbitration was by a third physician who was the chief of the department of Internal Medicine of the Medical Faculty of Prince of Songkla University, Hatyai, Songkhla province. Coronary artery diseases (CAD) included those with definite myocardial infarction (MI) which may also exhibit as sudden death (SD) or acute heart failure closely following an episode of chest pain. Cerebro-vascular diseases were all proven by brain imaging. CVD was a combination of CAD and cerebro-vascular disease. Heart failure was separated out in instances where it was deemed not related to ischemic heart (i.e. heart failure which resulted from infective endocarditis or of unknown etiology). Cancer was confirmed from histology or typical imaging (computer tomography). Death was considered indeterminate when the terminal phase could not be established from hospital records (*e.g.* a subject with known DM, poorly controlled, who had a record of having an infected foot and then reported as having died 6 months later without being admitted and the verbal autopsy was not available).

Data reduction and analysis

The cut-off values for the risk factors are described. Smokers were those currently smoking. HT was defined as those whose systolic blood pressure at screening $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg[19], being treated or had been diagnosed by a physician. DM had to have fasting plasma glucose (FPG) of $\geq$ 126 mg/dl[20], or was being treated or was informed by the physician as having DM but not needing pharmacologic treatment as yet. Several parameters for obesity were used: body mass index (BMI) $\geq$ 25 kg/m^2, waist hip ratio (WHR) of $\geq$ 0.90 in males and $\geq$ 0.85 in females and waist circumferences (WC) $\geq$ 90 cm for males and $\geq$ 80 cm for females[21,22]. For lipid, the cut-off values used were TC $\geq$ 200 mg/dl, TG $\geq$ 150 mg/dl, high density lipoprotein cholesterol (HDL-C) $\leq$ 35 mg/dl for males and $\leq$ 40 mg/dl for females and lastly TC/HDL-C of $\geq$ 5.0[23-25]. Low density lipoprotein cholesterol (LDL-C) was not calculated for the purpose of the present study.

Significant differences in characteristics between subjects whose vital status was known and

those lost to follow-up utilized the unpaired t-test for continuous data and chi-square test for categorical data. All p-values were based on two-tailed test of significance. The rate for death was normalized to per thousand person-years of follow up. Age-standardized mortality rates, for age 35-64 years were calculated with the use of the fifteen-year age-specific mortality and the age distribution of the WHO and new WHO world standard population[26,27]. Cox proportional-hazard models (on subjects who could be followed) were used to estimate the risks related to total, CVD and cancer deaths. The variables for adjustment were age, sex, religion, district, smoking, HT, obesity indices, DM and lipid levels. The analyses utilized STATA 7.0 statistical package (Stata Corp, College Station, Tx, USA).

Results

From the original 1,006 subjects, the status and events could be determined on 867 (86.2%). Among the 139 (13.8%) with unknown status, 119 (11.8%) were known to have moved out of the district, and 20 (2.0%) could not be traced (i.e. the authors do not know their whereabouts). The characteristics and the CVD risks when first screened among those with known and unknown status are shown in Table 1. Females exceeded males. Among the subjects with known status, about a quarter had HT, TC $\geq$ 240 mg/dl or low HDL-C. Those lost to follow-up tended to be non-Muslim, more urbanised and well to do with less prevalence of low HDL-C level.

During the follow-up period of 4,250 person-years, there were 50 deaths (Table 2A). The Kaplan Meier's 5-year survival rate was 94.3%. About a third of the deaths was from CVD and, another third was related to cancer. Six of the deaths could not be determined (4 of these had DM with complications but the exact cause preceding death could not be ascertained). Of the 6 cerebro-vascular deaths, 3 were from infarct and 3 from cerebral hemorrhage. This table (2A) also shows that half of the deaths occurred among those older than 70, hence the much lower mortality rates once age-standardized (Table 2B).

Table 3 shows the result of the Cox model adjusted for all variables. Independent factors common to total and CVD deaths were DM and HT while age $\geq$ 65 was a common factor for total and cancer deaths. In addition, smoking affected CVD death, and TG $\geq$ 150 mg/dl was a risk for cancer death. Gender, ethnicity (Malay Muslims vs. Thai-Chinese Buddhists), developmental status of the community, urbanization, TC and HDL-C were not contributory. Replacing the cut-off point of TC to 240 mg/dl did not make it independent.

Discussion

From the original 1,006 subjects, the status and events could be determined in only 86%. The

Table 1. Characteristics of the InterASIA-South subjects

Number of subjects	Known status n = 867	Lost to follow-up n = 139
Mean age, y	53.2 $\pm$ 11.8	54.5 $\pm$ 12.0
Male, %	36.4	40.3
Muslim, %	34.6	17.3*
Urban, %	44.1	84.2*
Income, Baht / month	6,785 $\pm$ 8,970	10,172 $\pm$ 15,367*
Smoking, %	20.8	20.9
Mean systolic BP, mmHg	123.7 $\pm$ 20.8	122.0 $\pm$ 19.1
Mean diastolic BP, mmHg	77.8 $\pm$ 12.5	76.1 $\pm$ 11.7
Hypertension, %	26.1	33.1
BMI $\geq$ 25 kg/m^2, %	41.8	47.5
Elevated WHR, %	43.1	48.9
DM, %	10.2	8.6
Total cholesterol $\geq$ 200 mg/dl, %	62.3	66.9
Total cholesterol $\geq$ 240 mg/dl, %	28.6	29.5
Low HDL-C, %	23.5	15.1*
Triglycerides $\geq$ 150 mg/dl, %	29.5	34.5
TC / HDL-C $\geq$ 5.0, %	39.8	31.6

* $p < 0.05$

Table 2A. Causes of death among the followed InterASIA-South subjects

Cause of death	Male n = 316	Female n = 551	Total n = 867	Dead ≥ 70 yrs
1. Cardiovascular disease	9 (39.1)*	7 (25.9)	16 (32.0)	
- coronary artery disease	5	5	10	4
- cerebro-vascular disease	4	2	6	5
2. Cancers	6 (26.1)	9 (33.3)	15 (30.0)	7
3. Others	8 (34.8)	11 (40.8)	19 (38.0)	
- Sepsis	3	0	3	2
- Renal failure	0	3	3	0
- COPD	1	1	2	0
- External**	0	2	2	2
- Other heart disease***	1	2	3	2
- Cannot be determined	3	3	6	4
Total	23 (100)	27 (100)	50 (100)	26

* Number of events (% of total death for that column)
** 1 suicide, 1 vehicular accident
*** 2 non-coronary heart failure, 1 infective endocarditis

Table 2B. The mortality rate of the followed InterASIA-South subjects

The mortality rate (per 1,000 subject years)	Male	Female	Both sexes
Crude death rate			
Total death	14.9	10.0	11.8
CVD death	5.8	2.6	3.8
Cancer death	3.9	3.3	3.5
Age-standardized rate			
Total death	5.2	7.4	6.4
CVD death	2.7	1.7	2.0
Cancer death	0.7	3.0	2.2

authors' experience showed that there were some subjects with transient domicile who volunteered for the examination and then disappeared. Despite the relatively short person-years of observation and the ability to trace the subjects, there are several features of the present cohort that are different from the only previous prospective study (EGAT) from Thailand[14,15]. The age of subjects at entry of 53 years contrasted with those of 42 years from EGAT, but this could have been offset by the interval of follow-up. Other differences included 64% females (vs. 23% from EGAT), 56% rural and 35% ethnic Malay-Thai. These urbanization and ethnicity were not specifically stated in the EGAT study, but unlikely to form significant proportions[14].

The present report shows that the prevalence of conventional CVD risks in the cohort that could be followed were 10% DM, 26% HT, 24% low HDL-C and 40% with TC/HDL-C greater than 5 (Table 1). The causes of death were dominated by CVD (32%) and cancer (30%). About half of the mortality from CVD and cancer were older than 70 years.

Independent factors for total death included age ≥ 65, HT and DM, and for death related to CVD, the factors were cigarettes, HT and DM. However, ethnicity (Malay vs. Thai-Chinese ancestries), type of community and gender did not independently contribute to death. As well, factors related to obesity and lipids, played no independent role with the exception of TG in cancer death. The lack of contribution of lipid parameters to death could be related to the low person-year of follow-up. However, the similarity to independent factors in EGAT with a much higher person-year (over 3,000 subjects and followed for 12 to 17 years)

Table 3. Risk factors for the varied death among the followed InterASIA-South subjects

	Total death			CVD death			CA death		
	Mortality rate[a]	HR (95% CI)	Adjusted HR[b] (95% CI)	Mortality rate[a]	HR (95% CI)	Adjusted HR[b] (95% CI)	Mortality rate[a]	HR (95% CI)	Adjusted HR[b] (95% CI)
Age 35-49 yrs	3.3			1.6			0.6		
50-64 yrs	10.5	3.22 (1.27-8.16)	2.22 (0.85-5.76)	2.5	1.52 (0.34-6.77)	0.70 (0.14-3.42)	4.3	7.96 (0.98-64.72)	7.56 (0.90-63.44)
$\geq$ 65 yrs	32.3	9.97 (4.10-24.22)	5.95* (2.33-15.16)	11.2	6.94 (1.88-25.62)	3.30 (0.80-13.72)	8.7	16.19 (1.99-131.59)	15.39* (1.74-136.32)
Sex (female : male)	9.6:14.9	1.55 (0.88-2.72)	1.32 (0.70-2.49)	2.6:5.8	2.26 (0.84-6.06)	1.38 (0.42-4.50)	3.3:3.9	1.17 (0.42-3.28)	1.31 (0.43-4.00)
Religion (Buddhist : Muslim)	11.2:12.2	1.10 (0.62-1.96)	1.12 (0.61-2.04)	4.7:2.0	0.44 (0.12-1.54)	0.44 (0.12-1.60)	2.9:4.8	1.66 (0.60-4.57)	2.88 (0.95-8.76)
Community (rural : urban)	9.6:13.9	1.44 (0.82-2.53)	1.14 (0.59-2.20)	2.5:5.4	2.13 (0.77-5.86)	1.46 (0.46-4.65)	2.1:5.4	2.56 (0.87-7.48)	2.44 (0.66-8.98)
Smoking	11.3:12.4	1.10 (0.56-2.16)	1.24 (0.58-2.63)	2.4:9.0	3.81 (1.43-10.15)	7.89* (2.36-22.40)	4.2:1.1	0.27 (0.04-2.07)	0.25 (0.03-2.06)
Hypertension	6.9:25.1	3.66 (2.08-6.42)	2.20* (1.17-4.15)	1.9:9.3	4.97 (1.80-13.67)	3.64* (1.06-12.45)	6.9:25.1	2.62 (0.95-7.22)	1.14 (0.38-3.44)
High BMI	12.2:10.7	0.88 (0.49-1.56)	0.68 (0.35-1.32)	4.0:3.4	0.83 (0.30-2.28)	0.88 (0.27-2.87)	8.5:6.8	1.58 (0.57-4.36)	1.21 (0.34-4.32)
High waist-hip ratio	7.0:17.6	2.53 (1.40-4.56)	1.39 (0.70-2.78)	1.6:6.6	4.04 (1.30-2.52)	2.66 (0.70-10.13)	4.3:12.5	2.02 (0.72-5.67)	0.71 (0.20-2.45)
Diabetes mellitus	9.1:33.8	3.73 (2.01-6.93)	2.13* (1.04-4.32)	2.6:14.5	5.62 (2.04-15.46)	5.12* (1.46-17.95)	9.1:33.8	2.34 (0.66-8.29)	0.85 (0.20-3.51)
High total cholesterol	8.7:13.2	1.51 (0.82-2.81)	1.13 (0.55-2.35)	3.1:4.2	1.33 (0.46-3.83)	1.56 (0.42-5.72)	8.7:13.2	1.66 (0.53-5.23)	0.71 (0.17-2.89)
Low HDL-cholesterol	10.7:14.2	1.32 (0.71-2.46)	1.19 (0.53-2.67)	3.7:4.0	1.10 (0.36-3.42)	2.05 (0.45-9.32)	7.7:8.4	0.83 (0.23-2.94)	0.49 (0.11-2.23)
High Triglyceride	10.0:15.2	1.52 (0.85-2.69)	0.96 (0.49-1.87)	4.0:3.2	0.80 (0.26-2.48)	0.28 (0.08-1.06)	10.0:15.2	3.59 (1.28-10.08)	3.60* (1.09-11.97)
High TC/HDL-C ratio	9.0:15.5	1.73 (0.99-3.03)	1.27 (0.62-2.60)	3.5:4.2	1.19 (0.44-3.20)	0.68 (0.18-2.59)	9.0:15.5	2.30 (0.82-6.46)	2.00 (0.56-7.09)

* p-value < 0.05, [a] per thousand-years, [b] adjusted for all variables in the table

suggests that person-year may not be the only reason[14,15]. The analysis from EGAT showed that for vascular deaths, positive risks were age, blood pressure, DM and cigarettes, similar to the present report[14]. For the 17-year follow-up of EGAT [15] and concentrating only on lipid factors, neither LDL-C nor TG predicted total, coronary nor vascular deaths, not unlike its 12-year follow-up which detailed other factors aside from lipids[14]. The model in the present study used low HDL-C as predictor, while EGAT evaluated HDL-C as a continuum and found it to be protective[14,15]. Differences in composition of the InterAsia-South and EGAT cohorts had been pointed out, i.e. urbanization, gender and ethnicity. The higher prevalence of low HDL-C among the Malay men was seen in the present study and one other southern survey[18,24]. Another country with Malays versus other ethnic groups is Singapore where there are three distinct (and rarely integrated) ethnic groups with different manifestations of coronary diseases. The rates of acute myocardial infarction in 1999 in the Singapore Myocardial Infarction Registry were significantly different among the ethnic groups: least among the Chinese (64.2 per 100,000 residents) then the Malays (148.1) and highest in the Asian Indians (205.0)[28], while the 28-day case fatality was highest among the Malays. Another report from Singapore which encompasses all admissions for coronary heart diseases (i.e. aside from myocardial infarction), showed the incidences in males (8.9 years of follow-up for a total of 24,986 person-years) also differed among the ethnic groups[29]. The Chinese and Malays had similar incidences (about 3.9-4.2 per thousand-subject years) but much lower than the Asian Indians (about 10.6 per thousand-subject years) with adjusted HR of Indians over the others of 3.1 (CI 2.0-4.8). The risks for developing coronary artery disease once adjusted for ethnicity, age and others showed that significant independent factors were DM (HR, CI = 1.7, 1.1-2.7) and HT (2.4, 1.6-2.7)[29]. However, despite the potential differences in HDL-C[13,30] among the ethnic groups, neither high LDL-C, low HDL-C, high TG, BMI nor cigarettes played an independent role in these coronary manifestations. Again, this lack of lipid contribution is not different from the analysis with the present cohort.

In conclusion, a five-year follow-up of 867 subjects from Songkhla province showed a similar rate of death for CVD and cancer. The independent risk factors for death did not include designated lipid risks or indices of obesity. Half of the deaths occurred among those older than 70 years old. This is the second

incidence study for death in Thailand and more study is needed.

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ปัจจัยเสี่ยงต่อการเสียชีวิตของประชากรในโครงการติดตามระยะยาว InterASIA-South

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วัตถุประสงค์: *เพื่อศึกษาอัตราการเสียชีวิตและปัจจัยที่เกี่ยวข้องต่อการเสียชีวิตของประชากรในโครงการ InterASIA จังหวัดสงขลา*

วัสดุและวิธีการ: *การติดตามระยะยาวนี้เป็นส่วนที่ทำต่อเนื่องจากโครงการ InterASIA ซึ่งศึกษาระดับของปัจจัยเสี่ยงต่อโรคหัวใจและหลอดเลือดในประชากรจีนและไทย เมื่อ พ.ศ. 2543 โดยในภาคใต้มีลักษณะพิเศษ คือ ประชากรที่ศึกษามีทั้งเชื้อชาติไทย-จีน (นับถือศาสนาพุทธ) และไทย-มาเลย์ (นับถือศาสนาอิสลาม) ข้อมูลการเสียชีวิตได้จากการทบทวนประวัติการรักษาในโรงพยาบาลร่วมกับการสอบสวนลักษณะการเสียชีวิตจากผู้ใกล้ชิดโดยเป็นข้อตกลงร่วมกันระหว่างแพทย์ 2-3 ท่าน และใช้สถิติ Kaplan Meier ในการวิเคราะห์*

ผลการศึกษา: *จากการติดตามเป็นเวลา 5 ปี ในประชากรตัวอย่างทั้งหมด 1,006 ราย พบว่าสามารถติดตามข้อมูลได้ร้อยละ 86 ในจำนวนนี้เสียชีวิต 50 ราย (อัตราการอยู่รอด 5 ปี เท่ากับร้อยละ 94.3) โดย 16 ราย เสียชีวิตจากโรคหัวใจและหลอดเลือด (10 รายจากโรคหลอดเลือดหัวใจ และ 6 รายจากโรคหลอดเลือดสมอง) 15 ราย เสียชีวิตจากมะเร็ง และครึ่งหนึ่งของผู้เสียชีวิตมีอายุมากกว่า 70 ปี ปัจจัยเสี่ยงต่อการเสียชีวิตจากทุกสาเหตุ ได้แก่ อายุ โรคความดันโลหิตสูง และเบาหวาน (เชื้อชาติไม่ใช่ปัจจัยเสี่ยง) ส่วนการเสียชีวิตจากโรคหัวใจและหลอดเลือด พบว่าภาวะน้ำหนักเกิน ระดับไขมันโคเลสเตอรอลรวม หรือไตรกลีเซอไรด์ ไม่เป็นปัจจัยเสี่ยง เช่นเดียวกับผลการศึกษาแบบติดตามไปข้างหน้าของพนักงานการไฟฟ้าฝ่ายผลิตหรือ EGAT แต่ในการศึกษานี้ไม่พบว่าระดับไขมันโคเลสเตอรอลชนิดที่มีความหนาแน่นโมเลกุลสูง (high density lipoprotein cholesterol) เป็นปัจจัยป้องกันแต่อย่างใด*

สรุป: *จากการติดตามในภาคใต้เป็นระยะเวลา 5 ปี ไม่พบว่าเชื้อชาติ การอาศัยในเขตเมือง หรือระดับไขมัน เป็นปัจจัยเสี่ยงต่อการเสียชีวิตแต่เบาหวานและความดันโลหิตสูง เป็นปัจจัยเสี่ยงต่อการเสียชีวิตที่สามารถปรับเปลี่ยนได้*