MASTER THESIS

The roles of Dietary Caffeine and Fish in the Risk of Non-Melanoma Skin Cancer in a Chinese population: The Singapore Chinese Health Study

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Statutory declaration

I declare that I have written this work independently and without assistance other than those specified sources, and have not used sources or means without declaration in the text. The Master Thesis was not used in the same or in a similar version to achieve an academic grading.

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Abbreviations

As: arsenic

BCC: basal cell carcinoma

CI: Confidence Interval

HR: hazard ratio

NMSC: non melanoma skin cancer

SCC: squamous cell carcinoma

UV: ultraviolet

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Summary

Background: Epidemiologic studies in populations of European descent suggest a possible chemoprotective effect of caffeine against nonmelanoma skin cancer (NMSC); but data in Asian populations are lacking. In addition, few population-based studies have addressed intake of different types of meat and NMSC.

Objectives: We examined the relationship of coffee, tea, and caffeine consumption; as well as different types of meat and seafood intake, with NMSC risk among Chinese in Singapore.

Methods: We used data from the Singapore Chinese Health Study, a prospective cohort of 63,257 men and women who were 45 to 74 years old at recruitment from 1993 to 1998. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by using multivariable Cox proportional hazard models.

Results: Coffee drinking was associated with reduced NMSC risk in a dose-dependent manner (P trend<.0001). Compared with those who drank coffee less than weekly, those who drank 3 or more cups per day had a lower risk of basal cell carcinoma (HR, 0.54; 95% CI, 0.31-0.93) and a lower risk of squamous cell carcinoma (HR, 0.33; 95% CI, 0.13-0.84). Compared with non-drinkers of black tea, daily drinkers of black tea also had a reduced risk of NMSC (HR, 0.70; 95% CI, 0.52-0.94). Caffeine intake reduced NMSC risk in a stepwise manner (P trend = .0025); subjects with a caffeine intake of 400 mg/d or more had the lowest risk (HR, 0.59; 95% CI, 0.34-1.04).

Fish intake was associated with increased squamous cell carcinoma (SCC) risk in a stepwise manner (P trend = 0.023); subjects in the highest quartile of fish intake had a 55% increased risk (HR=1.55, 95% CI=1.02, 2.34) compared to those with lowest quartile of fish intake. This positive association was not seen for intakes of shellfish, red meat (fresh and processed) and poultry. There was lack of association for intakes of fish, shellfish, red meat and poultry with risk of basal cell carcinoma.

Conclusion: Consumption of caffeinated drinks such as coffee and black tea may reduce the risk of NMSC among Chinese. Consumption of fish may increase the risk of SCC among Chinese in Singapore.

Introduction

Non-melanoma skin cancer (NMSC) is one of the most common cancers that inflict millions, and its incidence is on the rise worldwide.[1] Although the prognosis of NMSC is generally favorable compared to melanoma,[2] the public health burden of NMSC can be substantial due to its high incidence as well as cost of treatment.[3] In addition, up to 50% of patients with a primary basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) may develop one or more additional carcinomas within the next 5 years.[1]

The incidence of NMSC increases with age, and it is the highest among people with Fitzpatrick Skin Types I and II.[4] While the main environmental risk factor is ultraviolet (UV) radiation from the sun,[5] there has been great interest to identify other modifiable risk factors for skin cancer and new approaches for skin cancer prevention.

Coffee and tea are two of the most widely consumed beverages in the world.[6, 7] Due to their high global consumption, there is much interest in the effects of these caffeinated drinks on human health[8] and diseases, including skin diseases with generally poor prognosis such as melanoma.[9] Experimental evidence suggests that caffeine may have an anti-proliferative effect on keratinocytes via the induction of apoptosis in UV-damaged cells through multiple pathways.[10,11] A number of animal studies have consistently reported that caffeine intake or topical administration of caffeine on the skin inhibits UV induced skin cancer and tumors.[12] Recent meta-analyses on studies involving populations of European-descent have also provided evidence to support a possible protective role of caffeine against NMSC.[13,14]

Recently, two prospective cohort studies of nurses and health professionals in the U.S. reported an inverse association between red and processed meat intake and melanoma, and this was an unexpected finding since processed meat and potentially red meat might contain carcinogens.[15] Hence, the authors have cautioned that their findings need to be replicated in other populations.

Exposure to arsenic compounds have also been reported as a risk factor for NMSC.[16] Chronic arsenic poisoning is common in parts of the world where drinking water has high arsenic content, and increased prevalence of NMSC has been reported. [17,18] Arsenic tends to accumulate in the skin. Skin hyperpigmentation and hyperkeratosis have long been known to be the hallmark signs of chronic arsenic exposure, and there are significant associations between these dermatological lesions and risk of skin cancer.[19] Seafood has been found to be dietary sources of arsenic, although the exposure is generally much lower compared to exposure through contaminated groundwater.[20] A study in Singapore have shown the mean daily intake of arsenic compounds from seafood for a 60-kg person in Singapore reaches

3.1 μg/kg body weight/d. [21] The Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) determined the lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer (BMDL0.5) from epidemiological data to be 3.0 μg/kg body weight per day. [22] Arsenic is mainly derived from the fish component of a seafood diet, suggesting that Singaporeans are potentially at risk of arsenic toxicity over a lifetime from fish consumption. [21]

Skin cancer is the sixth most common cancer among men and the seventh most common cancer among women in Singapore.[23] The most common skin cancer is BCC, followed by SCC, with the highest incidence rates among the Chinese[24] who have Fitzpatrick Skin Types III and IV, compared to their Malay and Indian counterparts, who have darker skin tones. To explore the association between caffeine consumption, fish intake and the incidence of NMSC in the Chinese population, we conducted prospective analyses using data from the Singapore Chinese Health Study.

Methods

Study population

The current study was conducted in the Singapore Chinese Health Study, a population-based prospective cohort of 63,257 men (n=27,959) and women (n=35,298), aged 45–74 years at recruitment between April 1993 and December 1998. This study was approved by the Institutional Review Board at the National University of Singapore, and all enrolled participants gave written informed consent.

Baseline and dietary assessment

Caffeine Intake

At baseline, an in-person interview was administered to all participants using a structured questionnaire. We used a 165-item validated semi-quantitative food frequency questionnaire to record participants' habitual dietary intakes during the past year at enrollment. The details regarding the development and validation of the FFQ were reported previously.[25] For intake of coffee and tea, participants were asked in four separate questions, on average, how often they consumed 1) one cup of coffee (instant or freshly brewed), 2) one cup of "three-in-one preparation" coffee, 3) one cup of Chinese red tea or Ceylon tea (i.e. black tea), and 4) one cup of green tea, such as jasmine tea, and to pick their response from one of the nine predetermined categories: never or hardly ever, 1–3 cups a month, 1 cup a week, 2–3 cups a week, 4–6 cups a week, 1 cup a day, 2–3 cups a day, 4–5 cups a day, and 6 or more cups a day. The serving size of one cup of coffee or tea was assigned as 237 mL.

Dietary intake of caffeine and other nutrients was estimated from the Singapore Food Composition Database, which listed 96 nutritional and non-nutritional values per 100 g of the edible foods and beverages specific for this cohort. The foundation of this database relied heavily on the data published by the U.S. Department of Agriculture; and it was supplemented from multiple resources for other foods and components and referenced from published food composition tables from China, Malaysia, and Taiwan.[25] Coffee and tea accounted for 84% and 12% of total dietary caffeine intake in this cohort, respectively. The remaining minor contribution (4%) came from other caffeinated food sources such as soda (0.7%), cocoa drinks and chocolate-related food items.

Fish Intake

With regards to fish intake, the semi-quantitative food frequency questionnaire included 165 commonly consumed food items in this population. They were categorized into rice and noodle, meats (pork/beef/mutton, poultry, fish, and shellfish), vegetables, fruits, soy foods, legumes, dairy products, beverages, condiments, and preserved foods. The participants were instructed to select from eight frequency categories (ranging from "never or hardly ever" to "two or more times a day") and three portion sizes (small, medium, large) with the aid of photographs. The food frequency questionnaire was validated using two 24-hour recalls and re-administration of the food frequency questionnaire among 810 cohort participants. The correlation coefficient by these two methods for each dietary component ranged between 0.24 and 0.79, and the differences between mean values of most pairs for energy and nutrients were within 10% of each other's values.

Identification of cancer cases

Cancer diagnoses and deaths in this cohort were identified via linkage with the Singapore Cancer Registry and the Singapore Registry of Births and Deaths. As of 31 December 2016, only 56 (<0.1%) cohort participants were known to be lost to follow-up due to migration out of Singapore or other reasons. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases.[26] Since this was a study on the risk of cancer, we had excluded 1,936 participants with a history of invasive cancer at recruitment, and these were identified via self-report (n=822) or linkage with the nationwide cancer registry in Singapore (n=1,114), including 3 cases of melanoma and 15 cases of NMSC. As of December 31, 2016, among the 61,321 participants who did not have a history of cancer diagnosis at baseline, there were 632 incident cases of skin cancer diagnosed based on histopathologic confirmation. These included 427 BCC cases, 182 SCC cases, as well as 23 cases of melanoma, 24 cases of lymphomas, 7 cases of sarcomas, 5 cases of sebaceous adenocarcinoma, 4 cases of extra-mammary Paget's Disease and 13 cases of other rare cell types.

Statistical analysis

Caffeine

Person-years of follow-up were computed from the recruitment date to the date of BCC or SCC diagnosis, death, migration, or December 31, 2016, whichever occurred first. A series of Cox proportional hazards regression analyses were performed to examine the associations between exposures of our interest, namely coffee, black tea, green tea, sodas and caffeine, and skin cancer incidence. As coffee was the main contributor of caffeine intake in this population and a cup of coffee (237 ml) contained approximately 100 mg of caffeine, we created ordinal categories of caffeine intake to correspond to the categories of coffee consumption. We used hours sitting at work and watching TV as surrogates of duration for indoor activities, and also hours spent on moderate activities, strenuous sports, and vigorous work as surrogates of duration for outdoor activities in our analysis.

To control for confounding, the following were included as covariates in incremental models. Model 1 included gender, dialect group (Cantonese, Hokkien), age (years), and interview year (1993–1995, 1996–1998), education level (no formal education/primary, secondary or higher). Model 2 further included lifestyle factors such as cigarette smoking status (never, former, current), alcohol consumption (none/monthly, weekly, daily), body mass index (BMI) (<20, 20-<24, 24-<28, 28+ kg/m^2), time sitting at work (hours/day), time watching TV (hours/day), moderate activity (hours/week), strenuous activity (hours/week), vigorous activity (hours/week), and history of physician-diagnosed diabetes (yes, no). Model 3 further included all caffeinated drinks (coffee, black tea, green tea, soda) to examine the independent association of each caffeinated beverage with cancer risk.

Fish

The energy-adjusted intakes of individual food groups or items were computed using the residual method to control for potential confounding by total energy intake and to remove extraneous variation due to total energy intake. Person-years at risk were accrued from the date of recruitment to date of NMSC, loss to follow-up, death, or 31 December 2016, whichever occurred first. The quartile levels of each energy-adjusted intake of food or nutrient were derived from their respective distributions among all participants of in the cohort. The Cox proportional hazards regression method was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI) of developing NMSC for higher quartiles compared with the lowest quartile of food/nutrient intake. Two separate Cox models were employed with different sets of covariates: Model 1 (a basic model) included age (years), sex, year of baseline interview (1993–1995, 1996–1998), dialect (Hokkien/ Cantonese), and level of education (none, primary school, secondary school, or higher), and total energy intake (kcal/d). The inclusion of total energy intake in a model with energy-adjusted food items or nutrients was to further adjust for potential confounding effect by other unmeasured variables that may be relation to total energy intake such over- or under-reporting of dietary intake by participants. Model 2 included, in addition to variables in Model 1, smoking status (never, ex-smoker, current smoker), alcohol consumption (non-drinker/monthly drinker, weekly, daily), body mass index (20.0, 20.0–23.9, 24.0–27.9, >=28.0 kg/m2), physical activity (hours/week in moderate activity, hours/week in vigorous work, hours/week in strenuous sports), self-reported histories of physician-diagnosed diabetes (yes or no), and hours/day sitting at work, hours/day watching TV, and caffeine intake.

Results

After a mean [standard deviation (SD)] follow-up of 18.3 (5.7) years among a total of 61,321 participants (27,293 men and 34,028 women), 427 incident BCC and 182 SCC cases were identified via linkage with the nationwide cancer registry. The mean age (SD) at skin cancer diagnosis was 74.3 (8.9) years. Men accounted for 48.3% of all skin cancers.

Caffeine and NMSC

The study participants had a mean age of 56.4 years (SD 8.0) at baseline and 55.5 % were women. About 70.4% of our cohort participants reported drinking coffee daily, whereas 11.2% reported drinking black tea daily and 12.4% reported drinking green tea daily. Comparatively, soda was less frequently consumed; only 4.3% reported to drinking soda three or more times per week.

Table 1 shows the distribution of demographic characteristics of cohort members by the amount of daily caffeine consumption. Compared to the lowest quartile intake, those in the highest quartile of caffeine intake (≥400 mg/day) were more likely to be men, ever-smokers, engage in more hours of vigorous activities or strenuous sports per week, consume more alcohol, and have a lower prevalence of diabetes mellitus.

Table 2 shows the association between skin cancer incidence and the different types of caffeinated beverages in our study. Coffee drinking was associated with reduced NMSC risk in a dose-dependent manner (P-trend = 0.0001); compared with those who drank less than once a week, the risk was significantly reduced in daily drinkers and with increasing number of cups per day. In the highest intake category of ≥3 cups/day, the HR (95% CI) was 0.47 (0.29-0.75). Compared with non-drinkers (defined as drinking less than once a month), daily drinkers of black tea also had statistically significantly reduced NMSC risk (HR=0.70; 95% CI=0.52-0.94). We noted that the risk estimates were comparable for daily coffee drinkers of 1 to 2 cups (HR=0.74; 95% CI=0.61-0.89) and daily black tea drinkers (HR=0.70; 95% CI=0.52-0.94). However, due to the small number of daily black tea drinkers and since most of them drank only one cup per day, we were not able to analyze by the number of cups among daily drinkers of black tea. The intakes of green tea and soda were not significantly associated with NMSC risk.

Table 3 shows that the inverse association between coffee and cancer risk was present for both BCC and SCC. For black tea, while the association was statistically significant for BCC, it was not statistically significant for SCC, possibly due to the small number of cases (Table 3). Caffeine intake reduced overall NMSC risk in a stepwise manner (P trend = 0.0025); subjects in the highest caffeine intake category of >=400 mg/day had 41% reduced risk (HR=0.59, 95% CI=0.34, 1.04) compared to those with intake of <50 mg/day. This reduction in risk was observed for both BCC and SCC (Table 4). Finally, we did stratified analysis by gender to look for an interaction between gender and coffee, black tea and caffeine in association with NMSC risk. There was no heterogeneity in the results between men and women; all P for interactions ≥ 0.10.

Fish and NMSC

Table 5 shows the distribution of demographic characteristics of cohort members by the amount of daily meat intake. Compared to the lowest quartile intake, those in the highest quartile of fish intake (Q4) were more likely to be women, non-smokers, engage in fewer hours of vigorous activities or strenuous sports per week, consume less alcohol, and have a higher prevalence of diabetes mellitus. We have attempted to adjust for UV exposure by including durations of both indoor and outdoor activities as surrogate markers and covariates in the model.

Table 6 shows the association between skin cancer incidence and the different types of seafood and meat intake in our study. Overall fish intake was associated with slightly increased, but statistically non-significant higher risk of NMSC, although the results did not reach statistical significance (P-trend = 0.21). Intake of shellfish, red meat, processed meat and poultry were not associated with any increased risk of NMSC (Table 6).

Table 7 showed that association between various types of seafood and meat intake and risk of SCC. Fish intake was significantly associated with increased risk of SCC in a dose-dependent manner (P trend = 0.023) after adjustment for multiple potential risk factors; subjects in the highest fish intake category (Q4) had 55% increased risk (HR=1.55, 95% CI=1.02, 2.34) compared to those with intake category (Q1). This positive association of fish intake with increased SCC risk was not seen for intakes of shellfish, red meat (fresh and processed) and poultry. Table 8 showed that association between various types of seafood and meat intake and risk of BCC. There was no statistically significant association between intakes of fish, shellfish, red meat (fresh and processed) and poultry and risk of BCC.

Discussion

Caffeine and NSMC

In this large prospective cohort of middle-aged and elderly Chinese, we found that those who consumed coffee or black tea daily had a reduced risk of developing NMSC. Specifically, coffee drinking was associated with reduced risk of both BCC and SCC, while daily tea drinking reduced the risk of BCC. Overall, caffeine intake reduced the risk of both types of NMSC in a dose-dependent manner.

Experimental studies have provided evidence of an *in-vitro* pro-apoptotic effect of caffeine on keratinocytes.[10,11] Previous experimental studies have reported that caffeine has the ability to induce apoptosis in UV-damaged keratinocytes and in preventing UV-induced carcinogenesis in animals.[27] This photo-protective effect of caffeine has also been seen in cultured human keratinocytes.[10] Caffeine inhibits the UVB-induced formation of thymidine dimers and may enhance apoptosis of precancerous cells through p53-dependent and p53-independent biological pathways.[28] One of these pro-apoptotic pathways mediated by caffeine includes the inhibition of the ATR (ataxia telangiectasia mutated- and Rad3- related) protein,[29] which has preferential binding to UV-damaged DNA to obstruct premature chromatin condensation.[30] Our finding of a protective association of coffee and caffeine intake with BCC is consistent with all previous prospective studies in Australia,[31] USA[32] and Europe[33] that have examined the association between caffeinated coffee and BCC risk. Conversely, decaffeinated coffee has not found to be associated with BCC risk.[31,32]

To our best knowledge, this is the first prospective study to show an inverse association between coffee or caffeine and SCC risk, which contradicts the largely null associations from previous studies. The earliest cohort study looking at coffee and NMSC was conducted in a Norwegian population and it showed that coffee was associated with reduced risk of BCC but not of SCC.[33] In another study from Australia, with 323 cases of BCC and 196 cases of SCC, the authors reported that among those with previous skin cancer, those in the highest tertile intake of caffeine had reduced risk of BCC but not of SCC.[31] The Nurses Health Study and the Health Professionals Follow-up Study in the US also showed that using a reference group consisting of those who drank less than one cup a month, drinking two or more cups a day was associated with significantly reduced risk of BCC but not of SCC, and correspondingly, caffeine was inversely associated with risk of BCC but not of SCC in these two cohorts.[32] A hypothesis raised by these authors to explain the conflicting results with BCC and SCC is that SCC could have a lower DNA damage tolerance and lower apoptotic threshold compared to BCC,[34] and thus this could render SCC to be less susceptible to the apoptosis-inducing effect of caffeine. It has been observed that SCC in Asians has a greater tendency to occur in non-sun-exposed sites and a higher potential for metastasis compared to Caucasians, and a possible explanation is that whereas SCC is related to sun exposure among the fairer Caucasians, the development of SCC in darker-skinned Asians is more likely to be related to chronic scarring and areas of chronic inflammation.[35]

Population-based case-control studies in US populations have shown a protective effect of black tea drinking in the risk of SCC,[36] or of both SCC and BCC.[37] However, a recent Australian cohort study of 1,325 participants showed no associations between black tea intake and incidence of BCC or SCC.[31] Interestingly, a case-control study of SCC showed that the potential protective effect of black tea on cancer risk was related to multiple definitions or markers of strong tea such as reported strength of tea, brewing time and temperature.[36] Consistent with our hypothesis that the inverse association between black tea and risk of NMSC could be mediated by caffeine, given that the concentration of caffeine in green tea is generally lower than in black tea,[38] the lack of association between green tea and NMSC risk in our study is not unexpected.

The strengths of this study include the design of a population-based prospective cohort with a long follow-up time and a large number of incident NMSC cases, particularly BCC and SCC cases. This is also one of the few populations that allowed us to examine the intake of black tea and green tea separately. Inevitably, our study has limitations. One limitation is a possible misclassification of intake of caffeine, coffee or tea using the food frequency questionnaire and only measuring this at baseline. Another limitation is a lack of information on decaffeinated coffee or tea. Data on other potential confounders which are risk factors for NMSC, such as family history, history of radiation or chemical exposure, outdoor sun exposure, Fitzpatrick skin type and sunscreen use/protective outerwear were also not available. We have attempted to adjust for UV exposure by including durations of both indoor and outdoor activities as surrogate markers and covariates in the model. Although we did not ask about the use of sunscreen or other sun-protective practices during the recruitment, we do not suspect that such practices would be different between the participants.

In conclusion, our findings support experimental evidence that a high intake of caffeine could reduce the risk of NMSC. Specifically, the drinking of coffee was associated with reduced risk of SCC and BCC, and the drinking of black tea was associated with reduced risk of SCC. We hope our study can provide the impetus for further research to determine which component(s) of coffee/tea or whether caffeine is indeed the agent responsible for the chemoprotective effect.

Fish and NMSC

In this large prospective cohort of middle-aged and elderly Chinese in Singapore, fish consumption was associated with increased risk of developing SCC, in a dose-dependent manner. There was no association between fish consumption and the risk of NMSC or BCC. There was no significant association for consumption of shellfish, red meat (fresh and processed) and poultry with risk of NMSC, SCC or BCC.

There is extensive literature on ingestion of arsenic and increased incidence of NMSC, especially for squamous cell carcinoma.[39] Several regions around the world with high levels of arsenic-contaminated drinking water reported a dose-related relationship between arsenic exposure and NMSC.[40] In Chile (South America) and Taiwan (Asia), increased standard mortality ratios for NMSC among people in arsenic-endemic areas have been reported.[41,42] In a population-based case–control study among residents in New Hampshire, USA, a positive association was found between urinary measures of arsenic exposure and risk of SCC.[43] Another case-control study in East Europe found a positive association between residential water arsenic concentration and BCC risk.[44]

In populations where levels of arsenic in water are not substantial, the contribution of arsenic from food to total arsenic exposure becomes greater and more significant.[45] A study on “Global Burden of Disease for Skin, Lung, and Bladder Cancer Caused by Arsenic in Food” found that human exposures to arsenic through food is substantial (especially in fish and seafood), which is comparable to lower levels of arsenic in drinking water.[46] Seafood (fish and shellfish) is recognized as a major source of arsenic[47] and persistent organic pollutants.[48] Seafood is known to typically contain higher arsenic levels than other foods, although the toxic species (inorganic As) typically accounts for less than 2% of the total arsenic in seafood.[49] A study in Singapore reported that the mean daily intake of arsenic from seafood for a 60-kg person in Singapore reaches 3.1 μg/kg body weight/d, which is above FAO/WHO recommendations [21] , although the study did not characterize the species of arsenic present.[21] Most seafood consumed in Singapore is imported, principally from elsewhere in Asia such as Thailand and Malaysia. In a Malaysian study by Low et al, the trace metal concentrations in red tilapia fish (Oreochromis spp.) sampled from parts of Malaysia were analysed. Among the metals investigated, arsenic was found to be the key contaminant, which may have arisen from the use of formulated feeding pellets.[50] Hence, we hypothesized that our findings of increased SCC risk among those with high fish intake in our cohort could be the results of exposure to arsenic from in fish.

A recent paper that analysed two large cohorts of Caucasian nurses and health professionals, respectively, reported that higher red and processed meat intake had a modest inverse association with melanoma risk. However, because processed meat and potentially red meat might contain carcinogens,[51] the authors could not offer biological plausibility for their findings and emphasized the need for replication studies.[15] In our study, red meat intake (fresh and processed) did not show any association with NMSC risk. With regards to poultry, a study by Nigra et al indicates that the use of arsenicals in poultry production resulted in arsenic exposure to poultry consumers as measured in elevated urine total arsenic and DMA.[52] Again, in our study, poultry intake did not show any association with NMSC risk.

This is one of the few populations that allowed us to examine the intake of fish, shellfish, red meat, and poultry separately. Inevitably, our study has limitations. We did not have information on urinary arsenic concentrations among the cases and controls to see if levels correlated with fish intake or with the risk of SCC.

In conclusion, we found that high intake of fish was associated with increased risk of SCC in Singapore. The findings of our study provide an impetus for further investigation for the specific biological plausibility of consumption of arsenic-contaminated fish in the development of SCC in Singapore and other parts of the world.

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Table 1. Baseline characteristics of cohort participants [number (%) or mean ± standard deviation] by the amount of caffeine consumption

	Amount of daily intake			
Caffeine consumption	<50 mg	50-<250 mg	250-<400 mg	400+ mg
Participants	10330	42361	6634	1996
Skin cancer cases	124	421	50	14
Age at recruitment (years)	56.9 ± 8.4	56.4 ± 8.0	55.7 ± 7.6	55.5 ± 7.5
Men	3378 (32.7)	18518 (43.7)	4037 (60.8)	1360 (68.1)
Dialect				
Cantonese	4749 (46.0)	19631 (46.3)	3142 (47.4)	803 (40.3)
Hokkein	5581 (54.0)	22730 (53.7)	3492 (52.6)	1193 (59.7)
Secondary school or higher	2977 (28.8)	11818 (27.9)	2037 (30.7)	604 (30.3)
Ever smoker	1844 (17.9)	12729 (30.0)	2969 (44.7)	1196 (60.0)
BMI (kg/m^2)	23.0 ± 3.3	23.2 ± 3.2	23.2 ± 3.4	23.1 ± 3.4
Sitting at work (hours/day)	0.83 ± 1.3	0.92 ± 1.3	1.02 ± 1.4	1.03 ± 1.4
Watching TV (hours/day)	2.25 ± 0.9	2.26 ± 0.9	2.21 ± 0.9	2.18 ± 0.9
Moderate activity (h/wk)	0.99 ± 2.7	0.82 ± 2.5	0.99 ± 2.8	0.83 ± 2.7
Vigorous activity (h/wk)	0.31 ± 2.3	0.50 ± 3.1	0.98 ± 4.3	1.06 ± 4.4
Strenuous sports (h/wk)	0.18 ± 1.0	0.17 ± 1.0	0.24 ± 1.2	0.21 ± 1.1
Diabetes	1158 (11.2)	3689 (8.7)	492 (7.4)	130 (6.5)
Alcohol intake				
Non-drinkers	9690 (93.8)	37346 (88.2)	5464 (82.4)	1644 (82.4)
Weekly drinkers	466 (4.5)	3451 (8.1)	851 (12.8)	250 (12.5)
Daily drinkers	174 (1.7)	1564 (3.7)	319 (4.8)	102 (5.1)
Coffee (cups/week)	0.5 ± 0.9	9.5 ± 5.9	18.7 ± 7.5	31.5 ± 9.5
Green tea (cups/week)	0.4 ± 0.8	1.7 ± 4.2	6.6 ± 10.2	6.9 ± 12.5
Black tea (cups/week)	0.4 ± 1.0	1.5 ± 3.5	3.4 ± 5.9	2.8 ± 7.0
Soda (glasses/week)	0.3 ± 1.0	0.5 ± 1.9	1.2 ± 3.4	1.4 ± 3.8

[a]*P* values based on chi-square test for categorical variables and one-way ANOVA for continuous variables, all P values < 0.0001.

Table 2. The association between the different types of caffeinated beverages and the risk of NMSC in the Singapore Chinese Health Study (*n*=61,321)

	Cases	Person-years	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Coffee					
None to < weekly	154	226010	1.00	1.00	1.00
Weekly to <daily	59	102896	0.85 (0.63-1.14)	0.85 (0.63-1.15)	0.86 (0.64-1.16)
1- 2 cups/d	376	729636	0.76 (0.63-0.91)	0.76 (0.63-0.92)	0.74 (0.61-0.89)
3+ cups/d	20	64043	0.48 (0.30-0.77)	0.49 (0.30-0.78)	0.47 (0.29-0.75)
P for trend			0.0003	0.0004	0.0001
Black tea					
None to <monthly	419	713857	1.00	1.00	1.00
Monthly to <weekly	47	87532	1.00 (0.74-1.35)	0.99 (0.73-1.34)	1.00 (0.74-1.35)
Weekly to <daily	90	193858	0.87 (0.69-1.09)	0.87 (0.69-1.10)	0.87 (0.69-1.09)
Daily	53	127338	0.75 (0.56-1.01)	0.76 (0.57-1.01)	0.70 (0.52-0.94)
P for trend			0.039	0.04	0.015
Green tea					
None to <monthly	364	660272	1.00	1.00	1.00
Monthly to <weekly	72	130987	1.01 (0.79-1.31)	1.01 (0.78-1.30)	1.02 (0.79-1.32)
Weekly to <daily	96	193903	0.92 (0.74-1.16)	0.92 (0.73-1.15)	0.94 (0.75-1.18)
Daily	77	137423	0.94 (0.74-1.21)	0.93 (0.73-1.20)	0.91 (0.71-1.17)
P for trend			0.50	0.45	0.42
Soda					
1=<weekly	537	952586	1.00	1.00	1.00
once a week	21	57479	0.81 (0.52-1.25)	0.82 (0.53-1.27)	0.85 (0.55-1.32)
2-3 per week	32	62519	1.14 (0.80-1.64)	1.16 (0.81-1.67)	1.22 (0.85-1.75)
3+ per week	19	50002	0.88 (0.55-1.39)	0.89 (0.56-1.41)	0.92 (0.58-1.46)
P for trend			0.82	0.91	0.89

[a]Model 1: adjusted for age at recruitment, gender, dialect group, year of recruitment, education.

[b]Model 2: adjusted for variables in Model 1 plus body mass index, smoking, alcohol consumption, history of diabetes and hours spent sitting at work, at watching TV, in moderate activity, in strenuous sports, and in vigorous activity.

[c]Model 3: adjusted for all variables in Model 2, plus intake of black tea, green tea, coffee, and so

Table 3. Association between coffee and black tea intake and BCC or SCC in the Singapore Chinese Health Study (*n*=61,321)

Basal cell carcinoma	Cases	Person-years	HR (95% CI)
Coffee			
None to < weekly	106	225,000	1.00
Weekly to <daily	34	102,516	0.73 (0.49-1.07)
1- 2 cups/d	272	727,192	0.78 (0.62-0.98)
3+ cups/d	15	63,939	0.54 (0.31-0.93)
P for trend			0.017
Black tea			
None to <monthly	304	711,265	1.00
Monthly to <weekly	34	87,241	0.99 (0.70-1.42)
Weekly to <daily	51	193,172	0.69 (0.51-0.93)
Daily	38	126,969	0.74 (0.52-1.04)
P for trend			0.01

Squamous cell carcinoma	Cases	Person-years	HR (95% CI)
Coffee			
None to < weekly	48	224,351	1.00
Weekly to <daily	25	102,334	1.15 (0.71-1.87)
1- 2 cups/d	104	725,077	0.64 (0.45-0.91)
3+ cups/d	5	63,752	0.33 (0.13-0.85)
P for trend			0.001
Black tea			
None to <monthly	115	708,806	1.00
Monthly to <weekly	13	86,954	1.01 (0.57-1.80)
Weekly to <daily	39	193,056	1.30 (0.90-1.89)
Daily	15	126,697	0.62 (0.36-1.08)
P for trend			0.57

Adjusted for age at recruitment, gender, dialect group, year of recruitment, education, body mass index, smoking, alcohol consumption, history of diabetes, hours spent sitting at work, at watching TV, in moderate activity, in strenuous sports and in vigorous activity, plus intake of black tea, green tea, coffee and soda.

Table 4. Association between caffeine intake and the risk of NMSC in the Singapore Chinese Health Study (*n*=61,321)

			Model 1[a]	Model 2[b]
	Cases	Person-years	HR (95% CI)	HR (95% CI)
All skin cancers				
Caffeine intake (mg/day)				
0-<50	124	185,966	1.00	1.00
50-<250	421	778,614	0.80 (0.66-0.98)	0.81 (0.66-0.99)
250-<400	50	121,741	0.62 (0.45-0.87)	0.63 (0.45-0.88)
≥400	14	36,264	0.58 (0.33-1.01)	0.59 (0.34-1.04)
P for trend			0.0017	0.0025
Basal cell carcinoma				
Caffeine intake (mg/day)				
0-<50	87	185,224	1.00	1.00
50-<250	299	775,848	0.84 (0.66-1.06)	0.85 (0.67-1.08)
250-<400	30	121,359	0.57 (0.38-0.87)	0.59 (0.39-0.90)
≥400	11	36,217	0.70 (0.37-1.32)	0.76 (0.40-1.42)
P for trend			0.01	0.03
Squamous cell carcinoma				
Caffeine intake (mg/day)				
0-<50	37	184,620	1.00	1.00
50-<250	122	773,586	0.73 (0.50-1.06)	0.71 (0.49-1.03)
250-<400	20	121,234	0.71 (0.41-1.23)	0.67 (0.38-1.17)
≥400	3	36,072	0.35 (0.11-1.15)	0.33 (0.10-1.07)
P for trend			0.0498	0.03

[a]Model 1: adjusted for age at recruitment, gender, dialect group, year of recruitment, education.

[b]Model 2: adjusted for variables in Model 1 and body mass index, smoking, alcohol consumption, history of diabetes, hours spent sitting at work, at watching TV, in moderate activity, in strenuous sports, and in vigorous activity.

Table 5. Baseline characteristics of cohort participants [number (%) or mean ± standard deviation] by the amount of meat consumption

	Quartiles by fish intake			
Characteristics	Q1	Q2	Q3	Q4
Participants	15323	15315	15361	15322
Fish intake (g/d)	24.4 (14.8)	37.5 (13.8)	52.9 (13.9)	84.9 (28.9)
Age at recruitment (years)	56.5 (8.1)	56.7 (8.1)	56.5 (7.9)	55.9 (7.8)
Men	8152 (53.2)	6312 (41.2)	6187 (40.3)	6642 (43.4)
Dialect				
Cantonese	7527 (49.1)	7055 (46.1)	6928 (45.1)	6815 (44.5)
Hokkien	7796 (50.9)	8260 (53.9)	8433 (54.9)	8507 (55.5)
Education				
No formal education	10527 (68.7)	11087 (72.4)	11258 (73.3)	11013 (71.9)
Secondary school or higher	4796 (31.3)	4228 (27.6)	4103 (26.7)	4309 (28.1)
Ever smoker	5390 (35.2)	4430 (28.9)	4306 (28.0)	4612 (30.1)
BMI (kg/m^2)	22.9 (3.3)	23.1 (3.2)	23.2 (3.3)	23.4 (3.3)
Sitting at work (h/day)	0.95 (1.4)	0.89 (1.3)	0.89 (1.3)	0.94 (1.3)
Watching TV (h/day)	2.2 (0.9)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)
Moderate activity (h/wk)	0.82 (2.5)	0.80 (2.4)	0.87 (2.7)	0.98 (2.9)
Vigorous activity (h/wk)	0.71 (3.6)	0.49 (3.0)	0.48 (3.0)	0.48 (3.0)
Strenuous activity (h/wk)	0.22 (1.1)	0.17 (1.0)	0.16 (0.9)	0.19 (1.0)
Diabetes	1182 (7.7)	1336 (8.7)	1408 (9.2)	1543 (10.1)
Alcohol intake				
Non-drinkers	13128 (85.7)	13694 (89.4)	13791 (89.8)	13531 (88.3)
Weekly drinkers	1427 (9.3)	1148 (7.5)	1126 (7.3)	1317 (8.6)
Daily drinkers	768 (5.0)	473 (3.1)	444 (2.9)	474 (3.1)
Red meat intake (g/d),	29.4 (25.9)	27.7 (21.4)	30.0 (21.6)	35.2 (27.1)
Processed red meat intake (g/d)	3.1 (5.8)	2.5 (4.3)	2.4 (4.2)	2.8 (5.3)
Poultry intake (g/d),	20.7 (20.9)	18.8 (16.9)	19.8 (17.6)	23.0 (21.4)
Shellfish intake (g/d),	4.8 (5.1)	4.7 (4.6)	5.2 (4.9)	6.2 (5.9)

P values based on chi-square test for categorical variables and one-way ANOVA for continuous variables, all P values < 0.0001.

Table 6. The association between Non Melanoma Skin Cancer incidence and the different types of meat in the Singapore Chinese Health Study (*n*=61,321)

Food intake in quartile	Cases	Person-years	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Fish				
Q1	137	275725	1.00	1.00
Q2	155	278676	1.13 (0.90-1.42)	1.13 (0.90-1.43)
Q3	167	283943	1.22 (0.97-1.54)	1.22 (0.97-1.54)
Q4	150	284241	1.15 (0.91-1.45)	1.14 (0.90-1.44)
P for trend			0.18	0.21
Shellfish				
Q1	159	277531	1.00	1.00
Q2	153	277330	0.96 (0.76-1.20)	0.97 (0.77-1.22)
Q3	146	281471	0.96 (0.76-1.21)	0.98 (0.77-1.23)
Q4	151	286253	1.05 (0.84-1.32)	1.08 (0.86-1.36)
P for trend			0.66	0.51
Red meat				
Q1	168	282167	1.00	1.00
Q2	149	281187	0.88 (0.70-1.1)	0.88 (0.70-1.1)
Q3	153	279309	0.93 (0.74-1.17)	0.94 (0.74-1.18)
Q4	139	279922	0.91 (0.73-1.14)	0.91 (0.73-1.15)
P for trend			0.55	0.57
Processed red meat				
Q1	154	283389	1.00	1.00
Q2	171	281048	1.07 (0.85-1.36)	1.07 (0.85-1.36)
Q3	137	276995	0.86 (0.66-1.11)	0.86 (0.66-1.12)
Q4	147	281153	1.04 (0.82-1.32)	1.05 (0.83-1.34)
P for trend			0.86	0.92
Poultry				
Q1	159	275305	1.00	1.00
Q2	167	275388	1.02 (0.82-1.28)	1.03 (0.82-1.29)
Q3	137	282101	0.88 (0.69-1.12)	0.89 (0.70-1.13)
Q4	146	289790	1.00 (0.80-1.26)	1.00 (0.79-1.26)
P for trend			0.68	0.68

[a]Model 1: adjusted for age at recruitment, gender, dialect group, year of recruitment, education, energy intake.

[b]Model 2: adjusted for variables in Model 1 and body mass index, smoking, alcohol consumption, time sitting at work, time watching TV, moderate activity, strenuous activity, vigorous activity, diabetes, caffeine intake.

Table 7. The association between squamous cell carcinoma incidence and the different types of meat in the Singapore Chinese Health Study (*n*=61,321)

Food intake in quartile	Cases	Person-years	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Fish				
Q1	39	274415	1.00	1.00
Q2	40	277044	1.10 (0.70-1.72)	1.10 (0.70-1.71)
Q3	48	282333	1.34 (0.87-2.05)	1.34 (0.87-2.06)
Q4	55	283064	1.59 (1.05-2.40)	1.55 (1.02-2.34)
P for trend			0.017	0.023
Shellfish				
Q1	55	276157	1.00	1.00
Q2	40	275905	0.78 (0.51-1.19)	0.79 (0.52-1.2)
Q3	39	280041	0.82 (0.53-1.26)	0.83 (0.54-1.28)
Q4	48	284754	1.06 (0.72-1.57)	1.08 (0.73-1.61)
P for trend			0.75	0.68
Red meat				
Q1	51	280586	1.00	1.00
Q2	38	279725	0.80 (0.52-1.24)	0.80 (0.52-1.23)
Q3	46	277758	1.01 (0.66-1.52)	1.00 (0.66-1.52)
Q4	47	278787	1.05 (0.70-1.56)	1.03 (0.69-1.54)
P for trend			0.61	0.66
Processed Red meat				
Q1	62	282118	1.00	1.00
Q2	49	279367	0.82 (0.55-1.24)	0.82 (0.54-1.23)
Q3	36	275735	0.61 (0.38-0.98)	0.60 (0.38-0.97)
Q4	35	279636	0.69 (0.45-1.07)	0.69 (0.45-1.07)
P for trend			0.054	0.055
Poultry				
Q1	57	273997	1.00	1.00
Q2	44	273785	0.83 (0.55-1.25)	0.84 (0.55-1.26)
Q3	42	280804	0.85 (0.56-1.29)	0.86 (0.57-1.31)
Q4	39	288270	0.83 (0.55-1.25)	0.83 (0.55-1.26)
P for trend			0.39	0.42

[a]Model 1: adjusted for age at recruitment, gender, dialect group, year of recruitment, education, energy intake.

[b]Model 2: adjusted for variables in Model 1 and body mass index, smoking, alcohol consumption, time sitting at work, time watching TV, moderate activity, strenuous activity, vigorous activity, diabetes, caffeine intake.

Table 8. The association between basal cell carcinoma incidence and the different types of meat in the Singapore Chinese Health Study (*n*=61,321)

Food intake in quartile	Cases	Person-years	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Fish				
Q1	98	275177	1.00	1.00
Q2	115	278116	1.14 (0.86-1.49)	1.14 (0.87-1.49)
Q3	119	283279	1.18 (0.90-1.55)	1.18 (0.90-1.54)
Q4	95	283418	0.99 (0.75-1.32)	0.99 (0.75-1.32)
P for trend			0.97	0.97
Shellfish				
Q1	104	276702	1.00	1.00
Q2	113	276783	1.04 (0.79-1.38)	1.06 (0.80-1.39)
Q3	107	280974	1.03 (0.77-1.36)	1.05 (0.79-1.39)
Q4	103	285531	1.06 (0.80-1.39)	1.09 (0.82-1.43)
P for trend			0.75	0.60
Red meat				
Q1	117	281416	1.00	1.00
Q2	111	280644	0.91 (0.69-1.19)	0.91 (0.70-1.19)
Q3	107	278634	0.90 (0.69-1.19)	0.91 (0.69-1.20)
Q4	92	279297	0.85 (0.65-1.13)	0.86 (0.66-1.14)
P for trend			0.28	0.32
Red meat processed				
Q1	92	282473	1.00	1.00
Q2	122	280328	1.24 (0.93-1.66)	1.24 (0.93-1.66)
Q3	101	276505	1.02 (0.74-1.40)	1.03 (0.75-1.41)
Q4	112	280684	1.27 (0.95-1.69)	1.28 (0.96-1.71)
P for trend			0.29	0.25
Poultry				
Q1	102	274496	1.00	1.00
Q2	123	274748	1.13 (0.86-1.48)	1.14 (0.86-1.49)
Q3	95	281481	0.90 (0.67-1.21)	0.91 (0.68-1.21)
Q4	107	289264	1.09 (0.83-1.44)	1.09 (0.82-1.43)
P for trend			0.95	0.98

[a]Model 1: adjusted for age at recruitment, gender, dialect group, year of recruitment, education, energy intake.

[b]Model 2: adjusted for variables in Model 1 and body mass index, smoking, alcohol consumption, time sitting at work, time watching TV, moderate activity, strenuous activity, vigorous activity, diabetes, caffeine intake.

Appendix A

Participants were asked about their red meat intake through eight items comprising of "minced pork (or beef) patty and ball", "pork spareribs including bak kut teh", "pork satay", "other lean and fat pork slices, chops or cubes", "lean pork slices including char siew", "belly pork including siew yoke, pig trotters and pig skin", "pork liver", "mutton curry or mutton rendang", and "other pig organs such as intestines". Seven poultry items were listed as "deep fried chicken", "pan or stir fried chicken", "soy sauce chicken", "chicken satay", "boiled, stewed or roasted chicken", "chicken curry or chicken rendang", and "roasted or stewed duck or goose". The intakes of fresh fish and shellfish were asked through 6 items, "fish ball or cake", "deep fried fish", "pan or stir fried fish", "boiled or steamed fish", "shrimp or prawn", and "squid or cuttlefish". Intake of preserved or processed meat foods were also asked in 12 items comprising "Chinese sausage", "ham", "hot dog (pork or chicken)", "luncheon meat", "meat floss", "sweet barbeque meat", "salted fish", "anchovy", "dried fish", "other dried seafood", "canned tuna", and "canned sardine".

Acknowledgements

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