

Physical Exercise Protects against Risk of Cancer Death: A Case-cohort Study in a Health Check-up Population of 54,751 Taiwanese Men

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Abstract The effect of physical exercise level (PEL) on risk of cancer death has not been fully elucidated, especially in non-Western populations. The authors prospectively assessed whether increased PEL (ascertained from self-report questionnaire) was inversely associated with risk of cancer death in a case-cohort study, using data from the Taiwan Mei-Jao Cohort Study with 54,751 men aged 40 years or above and cancer-free at baseline (1996-2003). Their mortality status was ascertained via the Taiwan Death Registry through 2005. With up to 10 years of follow-up, 1,170 cases of cancer deaths were identified. A subcohort of 3,760 members was randomly selected. Compared to men with low PEL (physical exercise less than 1 hour/week), men with increased PEL had a significantly decreased risk of cancer death in a graded pattern, using multiple Cox regression analysis. Adjusting for age, body mass index, smoking, ethanol consumption, and betel chewing, hazard ratios for men with PEL 1-4 hours/week and > 4 hours/week were 0.77 (95% C.I: 0.68-0.89) and 0.82 (95% C.I: 0.73-0.92), respectively (p for trend < 0.01). The decreased risk was more significant in men less than 60 years of age than men at or above 60 years of age at baseline (p for interaction = 0.05). The association remained materially unchanged when excluding the first two years of follow-up. By system, decreased risk of death was observed for cancers of gastrointestinal tract and genitourinary tract, lung cancer, and all other cancers, except for blood cancer. By site, significantly decreased risks of death were observed for cancers of the liver and kidney. Increased PEL appeared to protect against risk of cancer death in this Taiwanese male health check-up population.

Keywords Exercise, Cancer death, Case cohort study, Asian, Health check-up

1. Introduction

Previous studies showed that higher level of physical activity appeared to be associated with a lower risk of certain types of cancer [1, 2] and overall cancer [3-8], though the results were not universally consistent [9-11]. After extensive literature review, the second World Cancer Research Fund / American Institute for Cancer Research Expert Report estimated that one third of cancers in Western high-income societies are attributable to factors related to food, nutrition, and physical activity. The report suggested that all forms of physical activity may prevent some types of cancer, including colon cancer, endometrial cancer, and postmenopausal breast cancer and made a specific recommendation that being daily physically active may prevent cancer [12, 13].

However, most of the studies were carried out among Western populations. Data from non-Western populations are extremely limited. A cohort study among a Japanese population suggested increased daily total physical activity was associated with lower risk of total cancer incidence in men and women, though physical exercise did not appear to have similarly strong protective effects [14]. In a cohort study among Chinese women, the authors observed overall physical activity (all forms) was associated with lower risk of all-cause death, including cancer death [15]. A population-based case-control study in Hong Kong found leisure-time physical activity was inversely associated with risk of cancer death in men and women, but the study was subjected to recall bias using proxy information [16]. A small-scale hospital-based case control study in Taiwan showed leisure-time physical activity was protective against colon cancer risk among men, but not among women [17].

Therefore, though it has been generally accepted that being physical active may prevent cancer in Western societies, the effects of physical activity on cancer risk remain unclear in non-Western populations. To further

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delineate how physical exercise alter risk of cancer death in Asian populations, we carried out this case-cohort study using data from the Taiwan Mei-Jao (MJ) cohort study.

2. Subjects and Methods

2.1. Subjects and Case-cohort Design, and Mortality Data Ascertainment

Baseline data were collected from the four nationwide MJ Health Screening centers in Taiwan. Details of the MJ centers were described elsewhere [18]. In short, the centers provide a multidisciplinary team approach for their members, with the annual health assessment performed by registered health practitioners. All subject data were recorded using standardized data sheets and entered into a database. It has been shown that the population structure of the Taiwanese adults that attended the health centers were similar to national data on adults published by our government [18, 19]. The Taiwan MJ Cohort Study was established through the following procedures. We recruited 60,316 men who were aged 40-80 years when taking the first health screen examination in 1996-2003. Men with missing data on body mass index (BMI), fasting plasma glucose, blood pressure, serum triglycerides, or high-density lipoprotein cholesterol (HDL-C), and with a history of cancer at baseline were excluded. As a result, we got 54,751 men for linkage to the Taiwan Death Registry (TDR) database using National ID numbers to ascertain their vital status in 1996-2005. Every cause of death was certified by a registered physician and recorded by a staff at the local health bureau. The causes of death were coded according to the ninth revision of the International Classification of Diseases (ICD-9) [23]. Among the 54,751 men, there were 3,034 men died in 1996-2005, including 1,181 men died of overall cancer (ICD-9 code 141-239). We initially took a random sample of 4,000 men as the subcohort for comparison. After exclusion of men with missing data on physical exercise (11 cases of cancer death and 240 subcohort members), we had 1,170 cases of overall cancer death and a random sample of 3,760 men as the subcohort (with 83 cases of overall cancer death included in the subcohort).

2.2. Date of Entry and Censoring

The date the patient received the baseline health exam in the MJ Centers defined the date of entry into the study. We used a case-cohort approach for data processing and analysis. For calculation of rates of cancer death, the number of cancer death cases in the entire cohort was used as the numerator, while person-months at risk (denominator), which was calculated as the duration from the date of entry until the end of the year 2005 for those who were alive or to the date of death for those who died, were estimated using the subcohort of 3,760 men.

2.3. Baseline Data Collection

Data on lifestyle factors, history of co-morbid conditions, current use of medication, and family history of cancer for each subject were self-reported and ascertained from a standardized questionnaire. The major exposure of interest in this study is physical exercise level (PEL). The participants were asked about the average amount of time they spend on physical exercise per week. Their PEL was classified into three categories: < 1 hour per week, 1-4 hours per week, and > 4 hours per week. The anthropometrics indices were measured and described elsewhere [20]. In short, height (measured to the nearest 0.1 cm) and weight (measured to the nearest 0.1 kg) was measured by an auto-anthropometer, Nakamura KN-5000A (Nakamura, Tokyo, Japan). BMI was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured twice, at a 10-minute interval, in the right arm using an auto-mercury-sphygmomanometer, with the participant in a sitting position after five minutes of rest. The mean of the two readings was used in this analysis. A venous blood sample was taken after 8 hours of fasting for measuring glucose, triglycerides, total cholesterol using an Hitachi 7150 [21].

Ethics approval for patient recruitment, data linkage and analysis was obtained from the Institutional Review Boards of Mennonite Christian Hospital in Taiwan, the TDR, the MJ health screen center, and Johns Hopkins Bloomberg School of Public Health.

2.4. Statistical Analysis

The mean values of anthropometric indices and proportions of potential confounders between cases and subcohort members were compared. Hazard ratios (HR) and corresponding 95 percent confidence intervals (CI) for cancer death were estimated using the Cox proportional hazards models processed with the 2005 Stata statistical software (Intercooled Stata 8.2; Stata Corporation, College Station, Texas), after testing of the proportional hazards assumption using scaled Schoenfeld residuals [22]. The main determinant of interest (PEL) did not violate the assumption. Standard errors were estimated using the robust Huber-White sandwich estimator to account for additional variance introduced by sampling from the cohort [23].

We evaluated modification of the PEL and cancer death association by entering a cross-product term of categorical PEL (≥ 1 hour vs. < 1 hour per week) and the possible modifier into a multivariable model, the coefficient for which was evaluated with the Wald test, and with stratified analyses of PEL by the corresponding categories. The potential effect modifiers we evaluated included age (≥ 60 vs. < 60 years), obesity (BMI ≥ 27 vs. < 27 kg/m^2), smoking (none vs. ever), alcohol (none/rare vs. often), and betel chewing (none vs. ever).

On the basis of significance in the age-adjusted analysis or significance in previous studies, risk factors selected for

evaluation in the multivariable models included age at baseline (continuous), smoking (none, former, current, categorical), alcohol consumption (none/rare, often, categorical), and betel chewing (never, ever, categorical). For the main analysis, the risk of deaths from overall cancer and site-specific cancer associated with baseline PEL ≥ 1 hour was compared to men with PEL < 1 hour. Tests for trends in risk of cancer death were assessed by fitting ordinal exposure variables as continuous terms. All hypotheses tests were two-sided with $p < 0.05$ deemed statistically significant.

3. Results

The median follow-up was 85.0 months (ranged from 0.7 to 120.0 months) for the subcohort members and 53 months (ranged from 0.6 months to 118.4 months) for the cancer death cases in the subcohort.

Mean fasting blood glucose was higher, while mean body mass index, and total cholesterol at baseline were lower for cases than for subcohort members. The cases tended to be older, had a family history of cancer and/or a history of co-morbid conditions including diabetes, hypertension, cardiovascular diseases, or cerebral vascular diseases. Compared to the subcohort members, the cases were more likely to be physically inactive and less well-educated; they were also more likely to be consumers of tobacco, alcohol, and betel nut (table 1).

With univariate analysis, age was a strong risk factor for cancer mortality. Smoking significantly increased risk of cancer death. Consumption of alcohol and/or betel nut was also associated with a significantly higher risk of cancer death. Obesity and hyperglycemia were not related to risk of cancer death. Men with higher PEL had a significantly lower risk of cancer death in a graded pattern (p -trend < 0.01). Compared to men with PEL < 1 hour/week, the age-adjusted hazard ratio of cancer death for men with PEL

1-4 hour/week and > 4 hour/week was 0.73 (95% confidence interval (CI), 0.64-0.83) and 0.76 (95% CI, 0.68-0.85) (table 2).

The inverse association between PEL and risk of cancer death appeared to be more significant among men below 60 years of age than among older men (p -interaction = 0.05). We observed no statistically significant difference in the association between PEL and cancer death following stratification by the other factors (table 3).

Compared to men with low PEL (< 1 hour/week), men with higher PEL (≥ 1 hour/week) at baseline were significantly less likely to die from overall cancer with a HR of 0.80 (95 percent CI: 0.72, 0.88), adjusting for age, obesity, smoking, use of alcohol and betel chewing. By system, there was no association between PEL and risk of death from blood cancer. The decreased risk associated with higher PEL was marginally significant for death from cancers of genitourinary (GU) tract and statistically significant for cancers of gastrointestinal (GI) system, lung cancer, and all other cancers combined. In site-specific analyses, there was a significant inverse association between high PEL and death from liver cancer and renal cancer, as well as a non-significant inverse association for death from cancer of the esophagus, stomach, gall bladder, pancreas, colon, rectum, and prostate (Figure 1). Additional adjustment for the presence of hepatitis B virus did not change the inverse PEL-liver cancer death association. Excluding men who died within the first two years of follow-up did not materially change the results (data not shown).

After adjusting for age, obesity, smoking, use of alcohol and betel chewing, an inversely graded response pattern was still observed between PEL and risk of death from overall cancer (p -trend < 0.01), GI cancer (p -trend < 0.01), lung cancer (p -trend = 0.02), GU cancer (p -trend 0.14), and all other cancers combined (p -trend = 0.08), but not for blood cancer (p -trend 0.36) (table 4).

Table 1. Characteristics of men who died of cancer and subcohort members at baseline, Taiwan MJ cohort study, 1996-2005

	Cases (n=1,170)		Subcohort (n=3,760)		p-value
	Mean (SD)	%	Mean (SD)	%	
Age (years)	62.8 (9.1)		54.8 (10.1)		< 0.01
Body mass index (kg/m ²)	23.7 (3.4)		24.2 (3.1)		< 0.01
Fasting plasma glucose (mg/dL)	108.8 (36.5)		106.8 (33.0)		0.1
Total cholesterol (mg/dL)	195.9 (39.9)		204.5 (37.6)		< 0.01
Family history of cancer*		26.5			0.1
Physical inactivity**		50.2		44.3	< 0.01
Education (less than high school)		66.8		49.4	< 0.01
Alcohol consumption (ever)		50.1		42.9	< 0.01
Betel nut usage (ever)		20.4		17.4	0.0
Tobacco smoking (ever)		67.2		54.8	< 0.01
Diabetes history		8.7		6.1	< 0.01
Hypertension history		20.9		16.6	< 0.01
Cardiovascular disease history		7.0		5.6	0.1
Cerebral-vascular disease history		2.3		1.5	0.1

Abbreviation: SD, standard deviation; hsCRP, high sensitivity C-reactive protein.

* Including cancer of nasopharynx, stomach, liver, colorectum, or prostate.

** Physical inactivity, exercises less than one hour per week.

Table 2. Hazard ratios and 95% confidence intervals for cancer death by selected characteristics, Taiwan MJ cohort study, 1996-2005

Variables	No. of cases	Person-months in subcohort	Age-adjusted HR	95% CI
Age				
40-59 y	409	205,049	1.00	Referent
60-69 y	488	71,254	2.69*	2.39 , 3.02
>=70 y	273	24,625	3.52*	3.10 , 4.00
p-trend			< 0.01	
Obesity				
No	977	250,866	1.00	Referent
Yes	193	50,063	1.07	0.94 , 1.22
Smoking				
Never	384	139,296	1.00	Referent
Past	204	46,561	1.17*	1.01 , 1.36
Current	582	118,071	1.52*	1.36 , 1.69
p-trend			< 0.01	
Alcohol				
None	584	168,184	1.00	Referent
Past/occasional	349	85,709	1.22*	1.09 , 1.37
Frequent	237	47,035	1.48*	1.30 , 1.68
p-trend			< 0.01	
Betel nut				
None	931	246,416	1.00	Referent
Past/occasional	153	39,056	1.52*	1.31 , 1.76
Frequent	86	15,456	1.99*	1.66 , 2.39
p-trend			< 0.01	
Exercise				
< 1 hr/week	587	134,910	1.00	Referent
1-4 hr/week	261	89,524	0.73*	0.64 , 0.83
> 4 hr/week	322	76,495	0.76*	0.68 , 0.85
p-trend			< 0.01	

Abbreviation: HR, hazard ratio; CI, confidence interval.

* $p < 0.05$.**Table 3.** Hazard ratios and 95% confidence intervals of cancer death for a higher physical exercise level (≥ 1 hour/week vs. < 1 hour/week) modified by selected variables, Taiwan MJ cohort study, 1996-2005

Variables	Age-adjusted HR	95% CI	<i>p</i> -interaction
Age			
<60 year	0.65	0.54 , 0.78	0.05
>=60 year	0.81	0.73 , 0.91	
Obesity*			
No	0.74	0.67 , 0.83	0.94
Yes	0.75	0.59 , 0.96	
Smoking			
None	0.71	0.60 , 0.85	0.49
Ever	0.78	0.70 , 0.88	
Alcohol			
None/rare	0.74	0.67 , 0.83	0.72
Often	0.76	0.62 , 0.95	
Betel nut			
None	0.76	0.68 , 0.85	0.55
Ever	0.86	0.66 , 1.03	

Abbreviation: HR, hazard ratio; CI, confidence interval.

* Obesity, body mass index ≥ 27 kg/m².

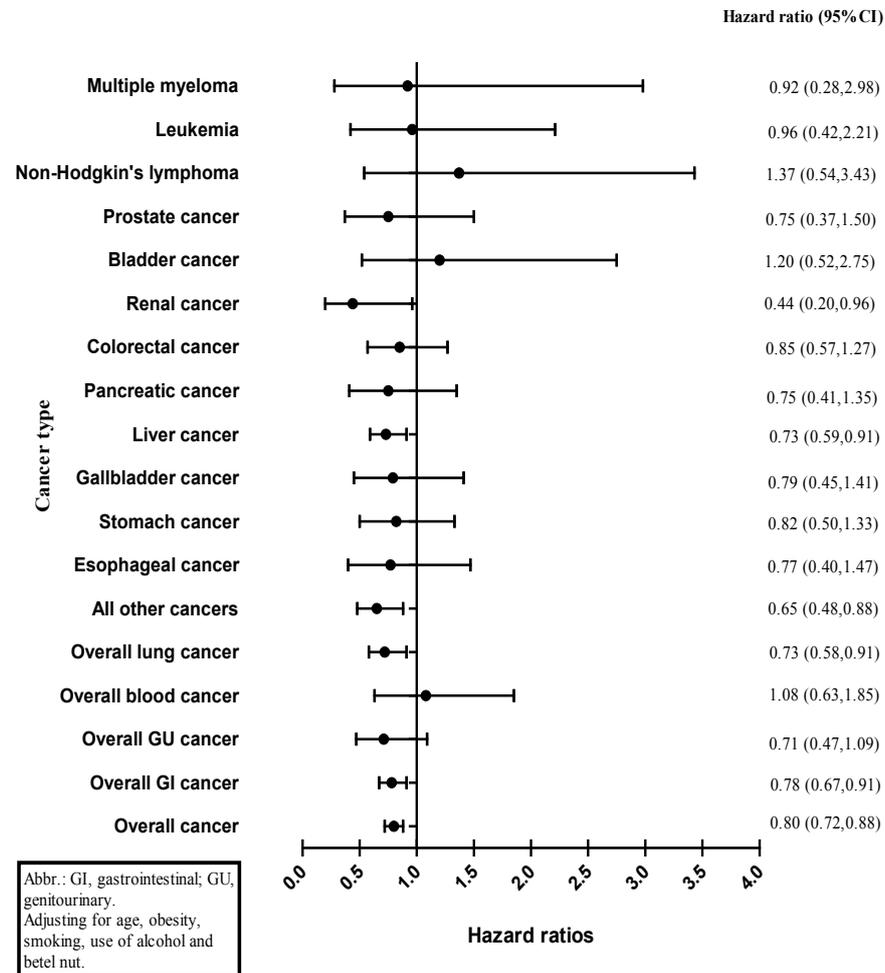


Figure 1. Multivariable-adjusted hazard ratios of physical exercise level (≥ 1 hour/week v.s. < 1 hour/week) for cancer death

Table 4. Multivariable-adjusted hazard ratios and 95% confidence intervals for death due to all cancers and various cancers by physical exercise level, Taiwan MJ cohort study, 1996-2005

Types of cancer	Person-months in subcohort	All participants			p trend
		Physical exercise < 1 hour/week	Physical exercise 1-4 hour/week	Physical exercise >4 hour/week	
<i>Overall cancer</i>	No. cases HR†	587 Ref.	261 0.77*	322 0.82*	< 0.01*
<i>GI cancer</i>	No. cases HR†	290 Ref.	143 0.80*	152 0.77*	< 0.01*
<i>GU cancer</i>	No. cases HR†	41 Ref.	20 0.74	24 0.69	0.14
<i>Blood cancer</i>	No. cases HR†	21 Ref.	11 0.77	26 1.32	0.36
<i>Lung cancer</i>	No. cases HR†	140 Ref.	59 0.70*	78 0.75*	0.02*
<i>All other cancers</i>	No. cases HR†	93 Ref.	28 0.53*	42 0.77	0.08

Abbreviation: HR, hazard ratio; GI, gastrointestinal; GU, genitourinary; Ref, reference.

* $p < 0.05$.

† HR adjusted for age (continuously), BMI (< 21 , 21-24, 24-27, > 27 kg/m², categorical), smoking (none, former, current, categorical), alcohol consumption (none/occasional, often, categorical), and betel chewing (never/ever, categorical).

4. Discussion

In this population-based prospective study of Taiwanese men, we observed a significant inverse association between PEL and risk of cancer death in a graded pattern. Compared to the counterpart, higher PEL was independently associated with 20% lower risk of cancer death during the up to 10-year follow-up period after accounting for a set of commonly accepted risk factors for cancer. The inverse association between PEL and risk of death was present not only for overall cancer, but also for most other types of cancers except for blood cancer. By sites, the inverse association between PEL and cancer death was strongest for renal cancer and liver cancer in our study.

We excluded men with a history of any cancer at baseline to reduce the possibility of spurious associations from reverse causation. The results were robust even after excluding the first two years of follow-up.

Though the beneficial effects of physical activity on risk of certain types of cancer have been reported by some researchers [1, 9, 17, 24-29], data on risk of overall cancer associated with physical activity are limited [14]. Five prospective mortality studies in Western populations found physical activity protected against risk of all-cause death including cancer death [3, 5, 8, 30, 31]. However, one other research group observed physical activity protected against cardiovascular death, but not cancer death [32]; and one report suggested physical activity protected against cancer death in men, but not in women [8]. Physical activity was inversely associated with risk of cancer incidence in two Western cohort studies [4, 7]. There are very few reports on this important issue from Asian countries. In a cohort study conducted in Japan, Inoue *et al.* reported daily total physical activity was inversely associated with incident cancer risk, especially in women, the elderly, and those who regularly engaged in regular physical exercise [14]. In a large-scale cohort study among 67,143 Chinese women, the authors found that although overall physical activity protected against all-cause death ($n=1,091$), the effects on cancer death ($n=537$) were not significant. With subgroup analysis, they showed non-exercise physical activity and cycling appeared to have non-significant protective effects on cancer death, however [15]. In a case-control study in Hong-Kong, the authors reported an inverse association between physical activity and risk of deaths from all-cause, cardiovascular diseases, and cancer. Yet the results might be subjected to recall bias because they had used proxy information on PEL [16]. The results of our prospective study are generally in line with the observations from Western populations and that from China and Japan.

Age, obesity [33, 34], smoking [35, 36], alcohol consumption [37, 38], and betel chewing (39) have been generally accepted as risk factors for some types of cancer or overall cancer. In our study, the protective effects of physical exercise appeared to be similar across categories stratified by the aforementioned factors except for age. The inverse association appeared to be slightly stronger among

the younger men than among the elderly (p -interaction = 0.05). In contrast, Inoue *et al.* found physical activity decreased more cancer risk among the elderly than among the younger. Orsini *et al.* in a cohort study showed a higher level of physical activity did not compensate the excess cancer mortality rate associated with overweight or obesity. Adjusting for all those risk factors did not materially change the inverse association between PEL and risk of cancer death in our study, however. Therefore, uncontrolled or residual confounding is unlikely to explain our findings. Our observations also indicate that physical exercise reduces cancer risk not only through improvement in obesity and other related factors, if any, but also through other mechanisms.

Some biological mechanisms through which physical exercise may decrease cancer risk have been proposed, though none is conclusive. Hyperinsulinemia is associated with a higher level of insulin-like growth factor-1 (IGF-1), which might play a vital role in promoting carcinogenesis, and a lower level of IGF-binding proteins (IGFBP). Exercise is associated with increased IGFBP-1 that binds free IGF and hinders their insulin-like action [40]. Exercise may improve insulin sensitivity and decrease fasting levels of insulin [41], as well as improve adiponectin levels [42, 43], all of which are associated with decreased cancer risk. Immune modulation may contribute to the protective value of exercise through changes in the activity of macrophages, natural killer cells, lymphokine activated killer cells, and regulating cytokines [44, 45]. Oxygen free radicals (OFR), which may play an important role in the expansion of tumor clones and the acquisition of malignant properties, is regarded as an important class of carcinogenesis. Exercise may slow or stop the loss of antioxidants that might counteract oxidative damage from ORF [46-48].

There were several strengths in this report. The study was conducted among a community-based Asian population that was free of cancer diagnosis. The prospective study design reduced potential bias caused by recall bias, reverse causation or survival bias. The sample size was large, enabling us to observe a graded inverse relation between PEL and cancer death. The standardized measurement of the baseline data minimized the possibility of information bias. And the results were robust after adjusting for common potential confounders and excluding the first two years of follow-up. The use of the relatively comprehensive TDR database to ascertain the death outcomes greatly reduced potential bias caused by losses of follow-up.

Some limitations of this study deserved attention. Misclassification of PEL may have been inevitable, because it was self-reported. However, since the data were collected before diagnosis of cancer, any misclassification was likely to result in underestimation of the association. Moreover, some men might have undiagnosed cancer at baseline that might have caused a lower PEL. Therefore, the possibility of spurious associations cannot be excluded. We had used only the baseline information for the PEL. Changes in PEL over time may have also biased the risk estimate toward the

null. Furthermore, though we have had adjusted for several potential risk factors for cancer, residual confounding is still possible due to unmeasured or imprecisely measured confounders. In addition, we conducted the study only among a male population. Some authors suggested that the exercise-cancer association might be sex-dependent [8, 14]. Our results may not be generalizable to female or other populations with a different general lifestyle or socio-economic level. Finally, we had no information on incident cancers. However, since cancer mortality is a function of cancer incidence and prognosis, we believe the decreased risk of cancer death associated with high PEL also indirectly indicated exercise might be inversely associated with risk of incident cancers and/or a more advanced form of cancers.

5. Conclusions

We concluded that in this community-based male population that was cancer-free at baseline, physical exercise was protective against cancer death, even after adjusting for a set of potential risk factors for cancer. We suggest that exercise programs deserve attention in cancer prevention.

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