European Journal of Human Genetics (2012) 20, 790–795

www.nature.com/ejhg

ARTICLE

Association between *survivin* −31G>C promoter polymorphism and cancer risk: a meta-analysis

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Survivin is an inhibitor of apoptosis protein and has a crucial role in the development of cancer. The *survivin* −31G>C (rs9904341) promoter polymorphism influences *survivin* expression and has been implicated in cancer risk. However, conflicting results have been published from studies on the association between *survivin* −31G>C polymorphism and the risk of cancer. To clarify the role of this polymorphism in cancer, we performed a meta-analysis of all available and relevant published studies, involving a total of 3485 cancer patients and 3964 control subjects. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations. The overall results indicated that the variant genotypes were associated with a significantly increased cancer risk (CC *vs* GG: OR=1.58, 95% CI=1.20–2.10; CC/GC *vs* GG: OR=1.23, 95% CI=1.00–1.51; CC *vs* GG/GC: OR=1.51, 95% CI=1.23–1.85). In the stratified analyses, significantly increased risk was associated with the Asian populations (CC *vs* GG: OR=1.67, 95% CI=1.16–2.40; CC *vs* GG/GC: OR=1.50, 95% CI=1.17–1.91). We also performed the analyses by cancer type, and no statistical association was observed. The results suggest that the *survivin* −31G>C promoter polymorphism might be associated with an increased risk of cancer, especially in the Asian populations.
European Journal of Human Genetics (2012) **20,** 790–795; doi:10.1038/ejhg.2011.276; published online 25 January 2012

Keywords: survivin; genetic polymorphism; carcinoma; susceptibility; meta-analysis

INTRODUCTION

It is well known that the incidence of cancer, which is a multifactorial disease that resulted from complex interactions between environmental and genetic factors,[1] has increased alarmingly. In addition, genetic variations may contribute to carcinogenesis. Signal transmissions resulting from these variations activate various pathways or mechanisms that disrupt the balance of normal cellular processes. Apoptosis is involved in the maintenance of these balances and has key roles in homeostasis.[2,3] Until now, two major apoptosis signaling pathways have been described: the extrinsic and intrinsic pathways.[4] These two pathways have independent groups of initiator caspases that transmit the death signal downstream but share the same group of effector caspases to execute the final cell death program.[4,5] Inappropriate regulation of apoptosis may lead to a number of human disorders, including cancer.[6]

Survivin, a member of the inhibitor of apoptosis protein family, is involved in inhibition of apoptosis and regulation of cell division.[7–9] Accumulating evidence has shown that increased expression of *survivin* favors the development and progression of malignancy by reducing tumor cell apoptosis.[10] The human *survivin* gene (also known as *BIRC5*), located on chromosome 17q25, consists of four exons spanning 14.7 kb.[11] In the promoter region of the *survivin* gene, the most widely studied polymorphisms are the G to C substitution at position −31 (*survivin* −31G>C, rs9904341, −31 from the first nucleotide of the ATG start codon). Xu *et al*[12] first investigated the role of this polymorphism in cancer cell lines and found the presence of the mutation correlated with increased *survivin* expression at both the mRNA and protein levels. They also showed that this mutation altered cell cycle-dependent transcription by modifying the binding motif of the cell cycle-dependent element (CDE)/cell cycle genes homology region (CHR) repressor, which is located in the proximal region of the *survivin* promoter.[12] Following this finding, researchers used *in vitro* promoter assays to demonstrate that the −31G allele had significantly lower transcriptional activity than the −31C allele, suggesting that the −31G/C polymorphism influences *survivin* expression, thus contributing to the genetic susceptibility to lung cancer.[13]

Recently, many studies have investigated the role of the *survivin* −31G>C polymorphism in the etiology of various type of cancers,[13–25] including lung, gastric, bladder, esophageal, colorectal, urothelial, and pancreatic cancer. However, the results of these studies remain inconclusive. To clarify the effect of variation in the role of *survivin* in cancer, we performed a meta-analysis of all eligible case–control and cohort studies to derive a more precise estimation of the overall cancer risk of the *survivin* −31G>C polymorphism and to quantify the potential for heterogeneity between studies.

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Received 28 March 2011; revised 27 December 2011; accepted 28 December 2011; published online 25 January 2012

MATERIALS AND METHODS

Identification and eligibility of relevant studies

Relevant publications were identified with a literature search using the keywords 'survivin', 'polymorphism', and 'cancer' in the Medline database (the last search update was 23 February 2011), and the research was limited to English-language journals. Additional studies were identified by a manual search of the references of original studies. The following criteria were used for inclusion of the identified articles in our meta-analysis: (1) a case–control or cohort design was used and (2) studies contained available genotype frequencies. The major reasons for exclusion of studies were: no usable data were reported. Finally, the data for this analysis were available from 13 case–control studies and one cohort study, totaling 3485 cancer cases and 3964 controls for the *survivin* −31C/G promoter polymorphism.

Data extraction

Two investigators independently extracted data and jointly reached a consensus on all of the studies researched. The following information was sought from each article: the first author's name, year of publication, country of origin, ethnicity, number of cases and controls, genotype frequencies for cases and controls, and Hardy–Weinberg equilibrium (HWE) of controls.

Meta-analysis

The strength of the association between the *survivin* −31G/C promoter polymorphism and risk of cancer was measured by odds ratios (ORs) with 95% confidence intervals (CIs). We examined the association between allele C of the *survivin* −31G/C polymorphism and cancer risk, and made comparisons with homozygotes (CC *vs* GG), heterozygotes (GC *vs* GG), the dominant genetic model (GC/CC *vs* GG), and the recessive genetic model (CC *vs* GG/GC). Trend analysis was performed across the three genotypes. Stratified analyses were also carried out by ethnicity and cancer type (limited to gastric and esophageal cancer). Heterogeneity assumption was evaluated with a χ^2-based *Q*-test. If the *P*-value was >0.05 of the *Q*-test, thus indicating a lack of heterogeneity among studies, then the effects model was used (the Mantel–Haenszel method).[26] Otherwise, the random-effects model (the DerSimonian and Laird method)[27] was performed. Funnel plots and Egger's linear regression tests were used to provide diagnosis of the potential publication bias. All statistical analyses were performed with the Stata software (version 9.2; StataCorp. LP, College Station, TX, USA), using two-sided *P*-values.

RESULTS

Characteristics of eligible studies

A total of 30 articles relevant to the search keywords were identified. Twelve of these articles did not explore the *survivin* −31G/C polymorphism and were excluded.[28–39] Four of these articles did not explore cancer risk and were excluded.[40–43] Finally, 13 case–control studies and 1 cohort study[44] that comprised a total of 3485 cancer cases and 3964 controls were included in our meta-analysis, and are presented in Table 1.

The 14 separate studies consisted of six Caucasians and seven Asian individuals. The genotype frequencies of the *survivin* −31G/C polymorphism were extracted from all eligible studies. The results of HWE test for the distribution of the genotypes in the control population are shown in Table 1. All the eligible studies were in HWE.

Quantitative synthesis

The frequency of C allele varied widely across the 14 studies, ranging from 0.33 to 0.53. As shown in Figure 1, the average frequency of the C allele in the Asian populations was 0.47, which was higher than in the Caucasian populations (0.38).

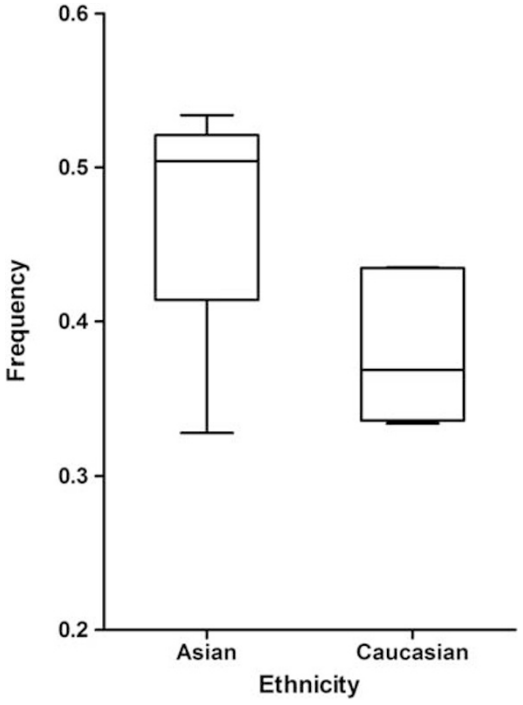

Figure 1 Survivin −31C allele frequency among controls as stratified by ethnicity.

Table 1 Characteristics of studies included in the meta-analysis

ID	*First author*	*Year*	*Country*	*Ethnic group*	*Cancer type*	*Case*	*Control*	*HWE*
1	Borbely	2006	Hungary	European	Cervical cancer	81	180	0.856
2	Kawata	2010	Japan	Asia	Bladder cancer	235	346	0.228
3	Borges	2010	Brazilian	Mixed	Gastric cancer	47	57	0.784
4	Theodoropoulos	2010	Greece	European	Pancreatic cancer	80	160	0.062
5	Wang	2009	China	Asia	Urothelial cancer	190	210	0.024
6	Jang	2008	Korea	Asia	Lung cancer	582	582	0.867
7	Gazouli	2009	Greece	European	Colorectal cancer	312	362	0.110
8	Yang	2009	China	Asia	Esophageal cancer	221	268	0.249
9	Upadhyay	2010	India	European	Esophageal cancer	250	250	0.094
10	Cheng	2008	China	Asia	Gastric cancer	96	67	0.667
11	Yang	2009	China	Asia	Gastric cancer	220	220	0.104
12	Bayram	2011	Turkey	European	Hepatocellular cancer	160	241	0.109
13	Ma	2011	China	Asia	Nasopharyngeal cancer	844	1021	0.357
14	Han	2009	USA	European	Ovarian cancer	167	/	/

Abbreviations: HWE, Hardy–Weinberg Equilibrium of Genotype of Control C, confirmed to HWE.

The *Q*-test of heterogeneity was always significant, and we conducted analyses using random effect models for the overall population. Overall, there was evidence for an association between increased cancer risk and the variant genotypes in different genetic models. As shown in Table 2 and Figure 2, the variant homozygote genotype CC was associated with significantly increased cancer risk (OR=1.58, 95% CI=1.20–2.10), compared with the wild-type homozygote genotype GG. In addition, increased cancer risks were also observed when we compared CC/GC *vs* GG (dominant model, OR=1.23, 95% CI=1.00–1.51) and CC *vs* GG/GC (recessive model, OR=1.51, 95% CI=1.23–1.85). Furthermore, the trend for the number of the C allele in the genotypes (the −31GG, −31GC, and −31CC genotypes) was statistically significant ($P<0.001$), indicating there was an evidence of a dose–response with increasing number of the variant allele. When stratified by ethnicity, increased cancer risk was found in the Asian populations (CC *vs* GG: OR=1.67, 95% CI=1.16–2.40; CC *vs* GG/GC: OR=1.50, 95% CI=1.17–1.91). We also performed the analysis stratified by gastric cancer and esophageal cancer, and no statistical association was observed.

Sensitivity analyses

Overall comparisons showed significant heterogeneity between studies, which may be due to grouping all cancer types together. We performed sensitivity analyses to assess the source of heterogeneity, which indicated that four independent studies[18,20,22,24] were the main origin of heterogeneity. This heterogeneity was effectively removed by exclusion of these four studies (CC *vs* GG: *P* heterogeneity=0.099; CC *versus* GG/GC: *P* heterogeneity=0.151; GC/CC *versus* GG: *P* heterogeneity=0.315). In addition, no other single study influenced the pooled OR qualitatively, as indicated by sensitivity analyses, suggesting that the results of this meta-analysis are stable.

Publication bias

To assess the publication bias of the literature, Begger's funnel plot and Egger's test were performed. As shown in Figure 3, the shapes of the funnel plots did not indicate any evidence of obvious asymmetry in all comparison models. Thus, Egger's test was used to provide statistical evidence of funnel plot symmetry and also did not show any evidence of publication bias ($t=0.36$, $P=0.729$ for CC *vs* GG; $t=0.25$, $P=0.806$ for CC *vs* GG/GC; $t=0.710$, $P=0.429$ for GC/CC *vs* GG).

DISCUSSION

The regulation of programmed cell death is important for the prevention of tumorigenesis. Impairment of apoptosis facilitates the accumulation of genetic errors by prolonging the cell cycle, promoting

Table 2 Meta-analysis of the Survivin −31C/G polymorphism and cancer risk association

		Sample size			*Test of association*				*Test of heterogeneity*		
Polymorphism	*Study*	*Case*	*Control*	N[a]	*OR (95% CI)*	Z	P-*value*	*Model*[b]	χ^2	P[c]	I^2 *(%)*
CC vs GG	Overall	1897	2018	14	**1.59 (1.20–2.10)**	3.20	0.001	R	44.27	<0.001	72.9
Ethnicity											
	Asian	1280	1353	7	**1.67 (1.16–2.40)**	2.73	0.006	R	27.74	<0.001	78.4
	European	578	636	6	1.47 (0.85–2.55)	1.36	0.173	R	14.59	0.006	72.6
Cancer type											
	Gastric cancer	197	166	3	2.20 (0.71–6.88)	1.36	0.173	R	10.51	0.005	81.0
	Esophageal cancer	253	271	2	1.32 (0.51–3.46)	0.57	0.568	R	6.34	0.012	84.2
GC vs GG	Overall	2514	3134	14	1.08 (0.90–1.28)	0.80	0.421	R	25.69	0.012	53.3
Ethnicity											
	Asian	1656	2072	7	1.32 (0.87–1.48)	0.92	0.358	R	18.40	0.005	67.4
	European	820	1013	6	1.06 (0.87–1.29)	0.60	0.548	F	6.24	0.182	35.9
Cancer type											
	Gastric cancer	252	277	3	1.06 (0.74–1.53)	0.34	0.736	F	4.66	0.097	57.1
	Esophageal cancer	369	415	2	0.99 (0.74–1.31)	0.09	0.925	F	0.00	0.947	0.0
CC/GC vs GG	Overall	3485	3964	14	**1.23 (1.00–1.51)**	2.00	0.045	R	39.23	<0.001	69.4
Ethnicity											
	Asian	2388	2714	7	1.32 (0.99–1.78)	1.86	0.063	R	26.18	<0.001	77.1
	European	1050	1193	6	1.18 (0.85–1.65)	0.98	0.328	R	11.97	0.018	66.6
Cancer type											
	Gastric cancer	363	344	3	1.38 (0.62–3.08)	0.79	0.429	R	9.48	0.009	78.9
	Esophageal cancer	471	518	2	1.06 (0.81–1.38)	0.39	0.696	F	0.65	0.421	0.0
CC vs GG/GC	Overall	3485	3964	14	**1.51 (1.23–1.85)**	3.90	<0.001	R	33.29	0.001	64.0
Ethnicity											
	Asian	2388	2714	7	**1.50 (1.17–1.91)**	3.24	0.001	R	18.96	0.004	68.4
	European	1050	1193	6	1.44 (0.91–2.29)	1.55	0.120	R	12.45	0.014	67.9
Cancer type											
	Gastric cancer	363	344	3	2.06 (0.91–4.66)	1.74	0.083	R	7.06	0.029	71.7
	Esophageal cancer	419	518	2	1.32 (0.50–3.50)	0.57	0.571	R	8.30	0.004	87.9

[a]Number of comparisons.
[b]Random-effects model (R) was used when *P*-value for heterogeneity test <0.05; otherwise, fix-effects model (F) was used.
[c]*P*-value of *Q*-test for heterogeneity test.
Bold values indicate significant difference.

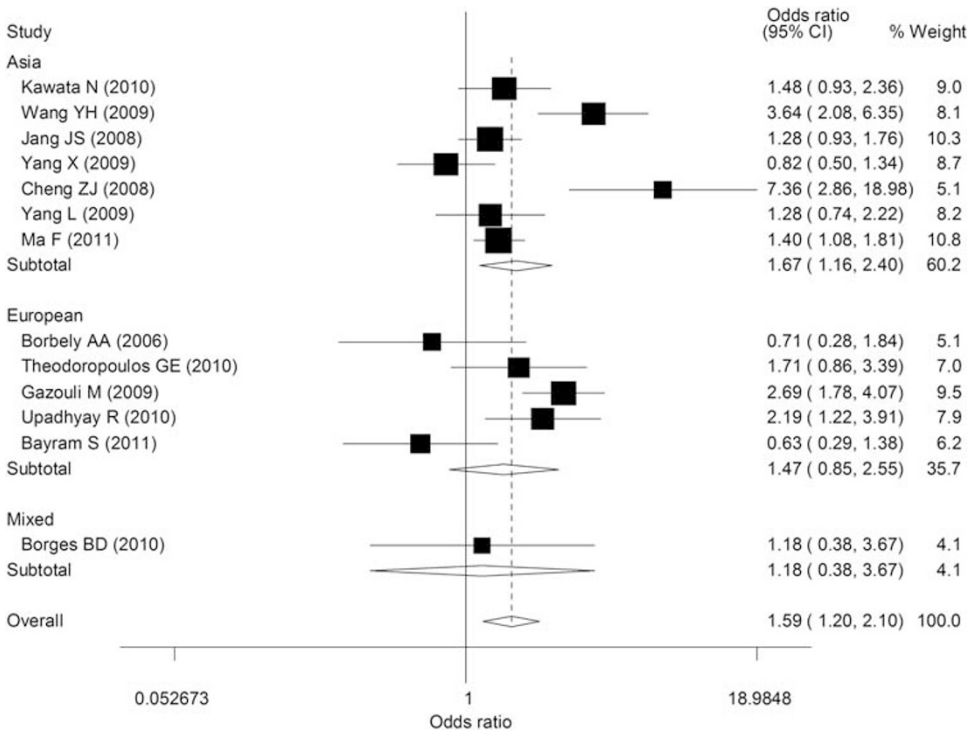

Figure 2 Forest plot showing the association between the survivin −31G>C promoter polymorphism and risk of malignancy (CC *vs* GG). The random effect model was used.

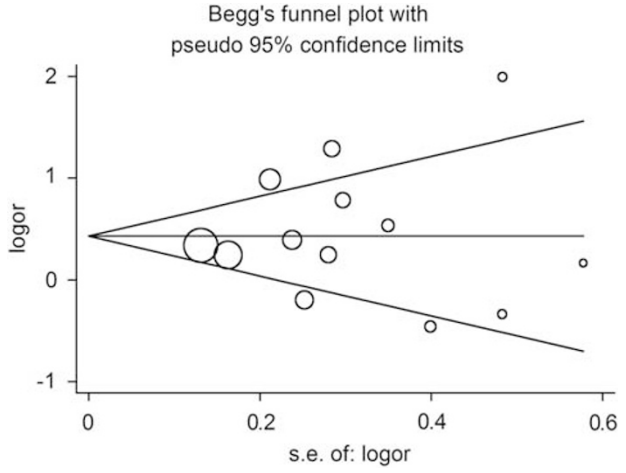

Figure 3 Begg's funnel plot for publication bias test, CC *vs* GG; each point represents a separate study for the indicated association. Log (OR): natural logarithm of OR. Horizontal line represents size of effect.

resistance to immune-based cytotoxicity, and providing selective growth advantages for the altered cells, thus contributing to carcinogenesis.[45,46] Survivin is an important apoptosis inhibitor protein and has a key role in inhibiting apoptosis and facilitating cell proliferation.[47] It has been observed that it is markedly overexpressed in almost all human malignancies, including lung, breast, brain, stomach, esophagus, and liver cancer, as well as ovarian and hematological cancers.[7,47] Therefore, it is biologically plausible that genetic variations of the *survivin* gene may modulate the risk of cancer.

The anti-apoptotic function of *survivin* has been identified both *in vitro* and *in vivo*.[48,49] The mechanisms through which *survivin* exerts this function are complicated, and includes binding to caspase-3 and caspase-7 to prevent their activation,[50,51] physically interacting with Smac/DIABLO to directly inhibit caspases,[52] and inhibiting the AIF pathway to provide cytoprotection to cells against caspase-independent cell death.[53] Regulation at the transcriptional level is an important mechanism for *survivin* expression. *Survivin* promoter activity is regulated by transcription factors such as β-catenin activated T-cell factor[54] and hypoxia-inducible factor-1 α.[55] In addition, *survivin* expression is also mediated by cell CDEs and cell CHRs located in the proximal region of the *survivin* promoter.[56,57] The −31G>C polymorphism of *survivin* is located at the CDE/CHR repressor binding site, and may influence the affinity of repressor binding to the CDE/CHR element.[12] Functional studies on this polymorphism have shown that the −31C allele has significantly higher transcriptional activity than the −31G allele, and individuals with the −31CC genotype have upregulated survivin levels compared with those with the GC and GG genotypes.[12,13] Thus, the −31G>C polymorphism may influence an individual's susceptibility to cancer. To date, several epidemiological studies have investigated the association between the −31G>C polymorphism in *survivin* and risk of various types of cancer but have produced conflicting results. In order to resolve this conflict, we conducted a meta-analysis of 14 studies, comprising a total of 3485 cancer cases and 3964 controls, to evaluate the associations between the −31G>C polymorphism and cancer risk.

Consistent with the observations made in the above-mentioned functional studies, our results suggested that variant genotypes (CC and CC/GC) were associated with a significantly increased cancer risk in several genetic models. In the subgroup analysis by ethnicity, we found that Asian individuals with the −31CC genotype had an increased risk of cancer when compared with GG or GG/GC genotypes. However, no significant association was found among Europeans. Several reasons may lead to this ethnic difference.

First, cancer is a multifactor disease with varying incidence in different populations. It has been suggested that this variation may depend on a combination of differences in polymorphism distributions with environmental factors.[58] For instance, the average frequency of the C allele in the Asian populations was 0.47, which was higher than in the Caucasian populations (0.38). Second, a smaller sample size was enrolled from European than from Asia, and together with lower frequency of risk allele (C) in Europeans than in Asians, may contribute to the non-significant findings of Europeans. However, these observations should be interpreted with caution as the number of European studies enrolled and the sample size of each study are limited and may be underpowered to detect a significant association. Moreover, obvious differences in composition of cancer types between European and Asian may also contribute to the findings observed. Last, other factors such as selection bias and different matching criteria may also have a role. Additionally, although no statistical association was observed in the subgroup analysis by cancer type, due to the wide CIs of our data, a possibility of an effect between genotypes and gastric or esophageal cancer risk may still exist. Therefore, more studies may be needed to clarify the effect of this polymorphism on cancer in European and on the difference between cancer types.

Some other limitations of our meta-analysis should be addressed. First, only papers written in English were included; studies published in other languages were not included, which thus may bias the results. Second, our lack of access to the original data from the included studies limited further evaluation of the potential interactions, as gene–environment and gene–gene interactions, and even different polymorphic loci of the same gene, may also modulate cancer risk. Third, our results were based on unadjusted estimates, while a more precise analysis needs to be conducted if individual data such as age and sex are available. Thus, lack of the information for the data analysis may lead to serious confounding bias. Nevertheless, advantages in our meta-analysis should also be acknowledged. First, a systematic review of the association of *survivin* polymorphism with cancer risk is statistically more powerful than any single study. Second, the studies included in our meta-analysis strictly and satisfactorily met our selection criteria.

Studies of common polymorphisms in genetic variations, if large enough and unbiased, can provide insights into the *in vivo* associations between the risk of cancer and genetic variation. Such studies may explore empirical associations that indicate that a polymorphism in a gene of interest has an influence on cancer, independent of metabolic regulatory mechanisms and other genetic and environmental variability.[59] Here, we performed a systematic literature review to evaluate the relationships between the *survivin* −31G>C promoter polymorphism and the risk of cancer. Individuals with variant genotypes of this polymorphism have an associated increased cancer risk, particularly those of Asian origin, which suggests that this increased risk may be ethno-specific. Additional larger studies are warranted to validate our findings. Future studies with larger numbers of standardized unbiased homogenous cancer patients and well-matched controls are required to examine associations between the *survivin* −31 G>C polymorphism and cancer risk and to draw more comprehensive conclusions. Moreover, investigations of the combined effects of gene and environment may lead to a better understanding of the role of the *survivin* −31 G>C polymorphism in cancers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the China Natural Science Foundation (30872657 and 81072078), Natural Science Foundation of Jiangsu Province (2008475 and 2010580), Scientific Program of Ministry of Health (W2011BX009), Program for Development of Innovative Research Team in the First Affiliated Hospital of NJMU, and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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