UNIVERSITI PUTRA MALAYSIA

SINGLE NUCLEOTIDE POLYMORPHISMS OF p53, p21, CYP1A1, FAS, AND BENZO(α)PYRENE AS RISK FACTORS IN CERVICAL CARCINOMA

TAN YEE HOCK

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By

TAN YEE HOCK

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

June 2017

Dedicated to my beloved family and loved ones

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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June 2017

Chair : Prof. Rozita Rosli, PhD
Faculty : Medicine and Health Sciences

Cervical cancer is the 3rd most common female cancer in Malaysia, constituting almost 7.7% of all female cancer cases. The main cause for the cervical cancer is human papillomavirus (HPV). However, infection with HPV is normally quiescent and can regress naturally rather than be integrated into the host genome. This suggests that there may be other cervical cancer risk factors such as the single nucleotide polymorphisms (SNPs) for critical regulatory genes p53 (codon 72), p21 (codon 31), CYP1A1 (MspI) and Fas (-670); and the polycyclic aromatic hydrocarbon benzo[α]pyrene. Currently, it is uncertain if these SNPs are cervical cancer risk factors in Malaysian females and how benzo[α]pyrene can be a risk factor through the activation of the CYP1A1 expression. Therefore, this study aims to investigate the SNPs of these genes; and benzo[α]pyrene as potential risk factors for cervical cancer.

SNPs are able to alter the expression of genes regulating apoptosis, cell cycle, cellular repair and xenobiotic metabolism towards favouring the malignant transformation of cervical cells. Using RFLP-PCR and statistical analysis, the relationship between the SNPs and risk for invasive cervical carcinoma was investigated for the first time in the multi-ethnic female population in Malaysia. The results showed a significant 3.7-fold (p=0.04) increase in risk for invasive cervical carcinoma for the p53 codon 72 Arg/Pro genotype in Chinese women when compared to the Arg/Arg genotype. Malaysian women carrying the p53 codon 72 Arg/Pro genotype were also significantly associated with a 2.8-fold (p=0.02) increase in risk for cervical adenocarcinoma when compared to the Arg/Arg genotype carriers. For the CYP1A1 MspI SNP, Malay women with the C/C genotype were significantly associated with 4.7-fold (p=0.03) increase in invasive cervical carcinoma risk compared to the T/T genotype carriers. Malaysian women with the C/C genotype were also 2.9-fold (p=0.02) more likely to develop cervical adenocarcinoma. No significant associations were found in the p21 codon 31 and the Fas -670 SNPs.

As for benzo[α]pyrene, it is a potential risk factor for cervical cancer due to its presence in the cervical mucus. To investigate the role of benzo[α]pyrene as a risk factor, a PCR array was used to analyse the gene expression of the apoptosis pathway genes in Ect1/E6E7 cervical cell lines after exposure to 1 μM of benzo[α]pyrene for 48 hours. Benzo[α]pyrene exposure in Ect1/E6E7 was found to increase gene expression of BCL-2 anti-apoptotic members, BCL2A1 and BCL-XL, by 4.21 and 2.91-fold, respectively. The gene expression of inhibitors of apoptosis BIRC3 and XIAP were also up-regulated by 2.86 and 2.09-fold, respectively. The gene expression of AKT1 which regulates cell survival and growth was also increased by 2.12-fold. While the gene expression of the death receptors (DR3, DR4 and DR5) was also up-regulated, there were no alterations in the gene expression of effector caspases.

In conclusion, the p53 codon 72 SNP, CYP1A1 MspI SNP and benzo[α]pyrene were identified as cervical cancer risk factors. The SNPs increased risk for cervical cancer in Malaysian Chinese and Malay women, respectively whereas exposure to benzo[α]pyrene promotes an anti-apoptosis response that potentiate the manifestation of cervical malignancies.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

POLIMORFISME NUKLEOTIDA TUNGGAL BAGI p53, p21, CYP1A1, FAS, DAN BENZO(α)PYRENE SEBAGAI FAKTOR RISIKO UNTUK KARSINOMA SERVIKS

Oleh

TAN YEE HOCK

Jun 2017

Pengerusi : Prof. Rozita Rosli, PhD
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Kanser serviks adalah salah satu kanser yang paling kerap dijumpai dan ia merangkumi sebanyak 7.7% daripada keseluruhan kes kanser di kalangan wanita di Malaysia. Punca karsinogenesis serviks adalah jangkitan virus papilloma manusia (HPV). Namun, jangkitan virus ini tidak semestinya mengakibatkan kanser serviks dan lebih kerap hilang tanpa dikesan daripada berintegrasi dengan genom hos. Ini menunjukkan bahawa terdapat faktor risiko lain bagi kanser serviks seperti polimorfisme nukleotida tunggal (SNP) bagi gen p53 (kodon 72), p21 (kodon 31), CYP1A1 (MspI) dan Fas (-670); dan polisiklik aromatik hidrokarbon benzo[α]pyrene. Pada masa ini, SNP yang dinyatakan masih belum dikenalpasti sebagai faktor risiko bagi kanser serviks di kalangan wanita Malaysia. Selain itu, kemungkinan benzo[α]pyrene sebagai faktor risiko melalui aktivasi ekspresi CYP1A1 juga tidak diketahui. Oleh itu, matlamat kajian ini adalah untuk menyiasat SNPs bagi gen yang dinyatakan serta benzo[α]pyrene sebagai faktor risiko yang berpotensi untuk mengakibatkan kanser serviks.

SNPs berkemampuan untuk mengubah ekspresi gen yang mengawal fungsi apoptosis, kitaran sel, pembaikian sel dan metabolisma xenobiotik sehingga menyebabkan transformasi malignan sel serviks. Dengan menggunakan RFLP-PCR dan analisis statistik, hubungan di antara risiko bagi kanser serviks dan SNP bagi gen p53 (kodon 72), p21 (kodon 31), CYP1A1 (MspI) dan Fas (-670) telah disiasat buat pertama kalinya di kalangan populasi wanita pelbagai etnik di Malaysia. Peningkatan signifikan untuk risiko kanser serviks sebanyak 3.7 kali ganda (p=0.04) telah dikesan bagi genotip Arg/Pro untuk p53 kodon 72 di kalangan wanita berbangsa Cina berbanding dengan genotip Arg/Arg. Wanita Malaysia yang mempunyai genotip Arg/Pro turut mempunyai peningkatan risiko sebanyak 2.8 kali ganda (p=0.02) untuk menghidapi adenokarsinoma serviks berbanding dengan genotip Arg/Arg. Bagi SNP CYP1A1 MspI, wanita berbangsa Melayu yang mempunyai genotip C/C mempunyai peningkatan risiko kanser serviks sebanyak 4.7 kali ganda (p=0.03) berbanding dengan genotip T/T. Wanita

Malaysia yang mempunyai genotip C/C turut mempunyai peningkatan risiko sebanyak 2.9 kali ganda (p=0.02) untuk menghidapi adenokarsinoma serviks. Tiada perubahan signifikan telah dikesan bagi SNP p21 kodon 31 dan Fas -670.

Bagi benzo[α]pyrene, ia merupakan faktor risiko yang berpotensi untuk kanser serviks kerana kehadirannya di dalam mukus serviks. Untuk menyelidik peranan benzo[α]pyrene sebagai faktor risiko, "PCR array" telah digunakan untuk menganalisa ekspresi gen dalam sel serviks Ect1/E6E7 selepas pendedahan kepada 1 μM benzo[α]pyrene selama 48 jam. Pendedahan sel Ect1/E6E7 kepada benzo[α]pyrene telah meningkatkan ekspresi gen BCL2A1 dan BCL-XL yang merupakan gen anti-apoptosis bagi keluarga BCL-2, masing-masing sebanyak 4.21 dan 2.91 kali ganda. Ekspresi gen BIRC3 dan XIAP, yang merupakan perencat apoptosis turut meningkat, masing-masing sebanyak 2.86 dan 2.09 kali ganda. Ekspresi gen AKT1 yang mengawal kemandirian and pertumbuhan sel juga meningkat sebanyak 2.12 kali ganda. Walaupun ekspresi gen bagi reseptor yang terlibat dalam apoptosis (DR3, DR4 dan DR5) turut meningkat, tiada perubahan dapat dikesan pada ekspresi gen bagi "effector caspase".

Sebagai kesimpulan, SNP p53 kodon 72, CYP1A1 MspI dan benzo[α]pyrene telah dikenalpasti sebagai faktor yang berisiko bagi kanser serviks. SNPs yang dinyatakan telah meningkatkan risiko kanser serviks di kalangan wanita Malaysia berbangsa Cina dan Melayu masing-masing manakala pendedahan kepada karsinogen benzo[α]pyrene telah menggiatkan respons anti-apoptosis yang boleh menggalakkan manifestasinya kanser serviks.

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I certify that a Thesis Examination Committee has met on 1 June 2017 to conduct the final examination of Tan Yee Hock on his thesis entitled "Single Nucleotide Polymorphisms of p53, p21, CYP1A1, FAS, and Benzo(α)Pyrene as Risk Factors in Cervical Carcinoma" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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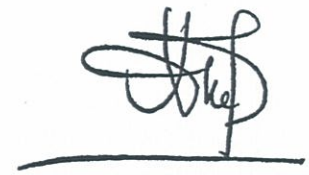

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3'UTR	3' untranslated region
95% CI	95% confidence interval
ADC	Adenocarcinoma
ADSC	Adenosquamous carcinoma
AHH	Aryl hydrocarbon hydrolase
AhR	Aryl hydrocarbon receptor
AIF	Apoptotic inducing factor
AKT	Protein kinase B
AP1	Activator protein 1
APAF-1	Apoptotic protease activating factor-1
Arg	Arginine
ARNT	Aryl hydrocarbon receptor nuclear translocator
ASR	Age standardized rate
ATP	Adenosine triphosphate
BAD	BCL-2 associated agonist of cell death
BAG3	BCL-2 associated athanogene 3
BAG4	BCL-2 associated athanogene 4
BAK/ BAK1	BCL-2 antagonist/killer 1
BaP	Benzo[α]pyrene
BAX	BCL-2 associated X
BCL-10	B-cell lymphoma 10
BCL-2	B-Cell CLL/Lymphoma 2
BCL2A1	BCL-2 related protein A1

BCL2L10	BCL-2 Like 10
BCL-W	BCL-2 Like 2/ BCL2L2
BCL-XL	BCL-2 Like 1/ BCL2L1
BID	BH-3 interacting domain death agonist
BIK	BCL-2 interacting killer
BIM	BCL-2 interacting mediator of cell death/ BCL2L11
BIR	Baculovirus IAP repeat
BIRC2	Baculoviral IAP repeat containing 2
BIRC3	Baculoviral IAP repeat containing 3
BIRC6	Baculoviral IAP repeat containing 6
BIRC8	Baculoviral IAP repeat containing 8
BLAST	Basic local alignment search tool
BPDE	7,8-dihydrodiol-9,10-epoxide/ benzo[α]pyrene diol epoxide
CAD	Caspase activated DNase
CARD	Caspase recruiting domain
CARD6	Caspase recruiting domain family member 6
CBM	CARMA1-BCL10-MALT1 complex
CD40LG	CD40 ligand
CDK	Cyclin dependent kinase
cDNA	Complementary DNA
cIAPs	Cellular inhibitor of apoptosis
CIN3	Cervical intraepithelial neoplasia grade 3
CYP1A1	Cytochrome P450, family 1, member 1
dAdo	Deoxyadenosine

DED	Death effector domain
DFFA	DNA fragmentation factor subunit alpha
dGuo	Deoxyguanosine
DISC	Death inducing signalling complex
DMBA	Dimethylbenz[α]anthracene
DMEM	Dulbecco's Modified Eagle medium
DMSO	Dimethyl sulfoxide
dNTPs	Deoxynucleotide phosphates
DR3	Death receptor 3/ TNFRSF25
DR4	Death receptor 4/ TNFRSF10A
DR5	Death receptor 5/ TNFRSF10B
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptors
FADD	Fas associated death domain
Fas	Fas receptor/ Apoptosis antigen 1/ Cluster of differentiation 95
FasL	Fas ligand
FBS	Fetal bovine serum
FFPE	Formalin fixed paraffin embedded
GDC	Genomic DNA control
GST	Glutathione S-transferase
H_2O_2	Hydrogen peroxide
HKG	Housekeeping gene
HPV	Human papillomavirus
HR-HPV	High risk human papillomavirus

HRK	Harakiri
HSIL	High grade squamous intraepithelial lesions
HSP70	Heat shock protein 70
IAP	Inhibitor of apoptosis proteins
IGF-1	Insulin-like growth factor 1
IKK	Inhibitor of κB kinase
IκB	Inhibitor of κB
JNKs	Jun N-terminal kinases
KSF	Keratinocyte serum free
LIF	Leukaemia inhibitory factor
LR-HPV	Low risk human papillomavirus
LSIL	Low grade squamous intraepithelial lesions
MAC	Mitochondrial apoptosis-induced channel
MALT	Mucosa associated lymphoid tissue
miRNA	Micro RNA
NAIP	NLR family-apoptosis inhibitory protein
NF-κB	Nuclear factor kappa B
NILM	Negative for intraepithelial lesions and malignancies
NOD	Nucleotide-binding oligomerization domain-containing protein
NOL3	Apoptosis repressor with CARD
NOXA	Phorbol-12-myristate-13-acetate-induced protein 1
OR	Odds ratio
p21	Cyclin dependent kinase inhibitor 1A
p53	Tumor suppressor p53

PAH	Polycyclic aromatic hydrocarbon
PBS	Phosphate buffered saline
PCNA	Proliferating cell nuclear antigen
PCR	Polymerase chain reaction
PERP	p53 apoptosis effector
PI3K	Phosphatidylinositol 3-kinase
PPC	Positive PCR controls
pRb	Phosphorylated retinoblastoma protein
Pro	Proline
PUMA	p53 up-regulator modulator of apoptosis
qPCR	Quantitative polymerase chain reaction
Rb	Retinoblastoma protein
RE	Restriction enzyme
RFLP	Restriction fragment length polymorphism
RIPK1	Receptor interacting serine/threonine-protein kinase 1
RIPK2	RIP-like interacting caspase-like apoptosis regulatory protein kinase
ROS	Reactive oxygen species
RTC	Reverse transcription controls
SCC	Squamous cell carcinoma
SDS-PAGE	Sodium dodecyl sulphate polyacrylamide gel electrophoresis
Ser	Serine
SNP	Single nucleotide polymorphism
SPSS	Statistical Package for Social Sciences
SQ	Semiquinone

STAT1	Signal transducer and activator of transcription 1
TBE	Tris/Borate/EDTA buffer
tBID	Truncated BID
TCDD	Tetrachlorodibenzo-p-dioxin
TGF-1	Transforming growth factor-1
TNF	Tumor necrosis factor
TNFR1	TNF receptor superfamily member 1A/ TNFRSF1A
TNFRSF10	TNF ligand superfamily member 10
TNFRSF11B	Tumor necrosis factor receptor superfamily member 11b
TNFRSF1A	TNF receptor superfamily member 1A
TNFRSF21	TNF receptor superfamily member 21
TNFRSF9	TNF receptor superfamily member 9
TNFSF8	Tumor necrosis factor superfamily member 8
TNFSF8	TNF ligand superfamily member 8
TP73	Tumor protein P73
TRADD	TNFRSF1A-associated death domains
TRAF-2	TNF receptor-associated factor 2
TRAF6	TNF receptor associated factor 6
TRAIL	Tumor necrosis factor ligand/ TNFRSF10
VDAC	Voltage-dependent anion channels
XIAP	X-linked inhibitor of apoptosis protein
$\Delta\Delta C_Q$	Delta-delta $\Delta\Delta C_Q$

CHAPTER 1

INTRODUCTION

Cancer is the manifestation of abnormal cellular growth which has the potential to metastasize and invade multiple regions of the body. The malignant disease can manifest itself in different regions of the body. Currently, the most common form of cancer worldwide originates from the lungs (12.9%), followed by the breast (11.9%), colorectum (9.7%) and prostate (7.9%). Cancer of the lung is most commonly found in men; constituting 16.7% , whereas breast cancer is the most commonly found cancer in women, constituting 25.2% (Ferlay *et al.*, 2015).

The presence of transformed cells however, does not indicate for certainty the onset of cancer. The detection of abnormal cells within the body triggers counteractive measures, primarily involving the induction of apoptosis or cellular death in order to terminate the afflicted cells. This process involves a myriad of genes, of which include the tumor suppressor gene p53, cyclin dependent kinase inhibitor 1 (p21), and tumor necrosis family member Fas (Haupt *et al.*, 2003). Simultaneously, the xenobiotic metabolizing gene CYP1A1 is also actively eliminating carcinogenic compounds within the body that is capable of inducing abnormal transformation in cells (Crofts *et al.*, 1994; McCann *et al.*, 1992). Proper regulation of these genes is therefore essential towards minimizing abnormal changes within cells. However, minor changes to the human genetic makeup can potentially disrupt the functions of these cells.

These genetic changes can be resulting from human evolution which over-time, induce subtle changes in the genetic makeup which are unnoticed. The selection of a particular trait for human survivability can unknowingly predispose humankind to certain long term complications. These subtle changes can be nucleotide substitutions which result in the production of an altered amino acid, functionally different from its wild-type counterpart. These nucleotide substitutions are known as single nucleotide polymorphisms (SNPs) and causes DNA sequence variation found in more than 1% of the population (Joseph *et al.*, 2006). While mutations are also used to describe alterations in DNA sequences, these normally exist as single individual cell events less commonly found in the population.

The four earlier mentioned genes each contain SNPs that are able to alter the functions of the gene. In fact, the SNPs found on codon 72 of p53, codon 31 of p21, position 3801 of CYP1A1 and position 670 of Fas genes had been previously reported to alter the expression of their respective genes (Kanemitsu *et al.*, 2002; Thomas *et al.*, 1999; Bunz *et al.*, 1998; Kiyohara *et al.*, 1996). For example, the p53 codon 72 SNP has been reported to produce a variant protein which is biologically and biochemically different from its wild type counterpart (Thomas *et al.*, 1999; Matlashewski *et al.*, 1987). This may alter the level of cellular apoptosis, cell senescence and cell cycle arrest regulated

by p53 (Jin and Levine, 2001). The activation of the p21 gene may also be affected since both p53 and p21 are known to work in unison to regulate cell cycle arrest, which is important in the prevention of the proliferation of abnormal cells (He *et al.*, 2005; Bunz *et al.*, 1998). As for CYP1A1, the MspI polymorphism of CYP1A1 alters the metabolic activity of the CYP1A1 enzyme resulting in a higher level of reactive metabolites produced from the breakdown of the polycyclic aromatic hydrocarbon of tobacco, among which includes the carcinogen benzo[α]pyrene, to a level which may be improperly catalysed by the detoxification system (Kiyohara *et al.*, 1996). In addition, the SNP location for Fas -670 SNP is located at the same binding region where Fas mediated apoptosis is initiated and may alter the apoptosis potential of Fas (Sibley *et al.*, 2003). Hence, the deregulation of these SNPs can promote the growth of abnormal cells, leading to malignant diseases such as cervical cancer.

Cervical cancer is the 4th most commonly found cancer in women worldwide, constituting almost 8% of all cancer cases (Ferlay *et al.*, 2015). In the multi-ethnic nation of Malaysia, cervical cancer was the 3rd most common cancer for the period of 2007 to 2011, being most prominent in Chinese women (Azizah *et al.*, 2016). The carcinogenesis of the cervix requires the presence of an external etiological agent known as the human papillomavirus (HPV) (zur Hausen and de Villiers, 1994). However, HPV infections are capable of regressing over time indicating that other risk factors such as SNPs of the aforementioned genes may have a role in the manifestation of cervical cancer.

Aside from that, the existence of harmful chemicals in the environment can also propagate the manifestation of malignant growth in the human body. These chemicals exist as polycyclic aromatic hydrocarbons (PAH), organic compounds consisting only of carbon and hydrogen which are released through the incomplete combustion of organic matter (Guo *et al.*, 2011). Some examples of PAHs are naphthalene, benz[α]anthracene, fluoranthene and the well-known benzo[α]pyrene (BaP) (Abdel-Shafy and Mansour, 2016).

BaP is formed from the incomplete combustion of carbon based products such as tobacco smoking (Ribiere *et al.*, 2016). It has been classified as a class one carcinogen by the International Agency for Research on Cancer (IARC). More importantly, it has been previously detected in the cervical mucus of females who are routinely exposed to tobacco smoke, indicating that it could be a risk factor for cervical cancer (Melikian *et al.*, 1999a; Prokopczyk *et al.*, 1997). These exposed cells are more likely to develop abnormal transformation and undergo apoptosis. BaP exposure had triggered mitochondrial regulated apoptosis in the mouse hepatoma Hepa1c1c7 and the human lung cancer H460 cell lines (Xiao *et al.*, 2007; Ko *et al.*, 2004). However, the apoptosis response induced by BaP had not been widely studied in human cervical cells and was therefore a point of interest.

Thus, the problem statement of this study is as follows:

a) The p53 codon 72, p21 codon 31, CYP1A1 MspI and Fas -670 SNP association with cervical cancer are yet to be established in the Malaysian female population. Population studies worldwide suggest that certain SNPs are associated with cervical carcinoma and that the association may be population dependent. Given that SNPs may be potential risk factors for cervical carcinoma alongside HPV infection, population specific SNP studies are required to elucidate the association between the aforementioned SNPs and cervical cancer risk in the Malaysian population.
b) Prior BaP studies on cancer cell lines have reported that the exposure to BaP causes apoptosis. This suggests that BaP may be able to alter the regulation of apoptosis in cell lines, cumulating in the selection of a pro-survival or a pro-apoptosis response which can decide the fate of the affected cells. However, BaP's role as a risk factor in non-malignant human cervical cell lines is yet to be established. Hence, it is essential to identify BaP's role as a risk factor in non-malignant human cervical cell lines as the presence of BaP metabolites has been detected within the cervical mucus.

It is hypothesized for this study that certain SNPs are able to significantly alter the risk for invasive cervical cancer and that certain ethnic groups are more likely to develop cervical cancer. As for BaP, it is hypothesized that exposure to BaP causes the up-regulation of genes involved in apoptosis thereby causing programmed cell death.

Thus, the general objective of this study is to investigate the single nucleotide polymorphisms of p53 codon 72, p21 codon 31, CYP1A1 MspI, Fas -670; and benzo[α]pyrene as potential risk factors for cervical cancer.

The following are the specific objectives:

a) To establish the SNPs prevalence for the aforementioned genes in the three main ethnic groups of Malaysia
b) To determine whether the SNPs predisposes women of certain Malaysian ethnic groups to cervical cancer
c) To identify the apoptosis response of Ect1/E6E7 cervical cell line after exposure to benzo[α]pyrene
d) To quantitate the gene expression fold change of the apoptotic pathway genes in Ect1/E6E7 after exposure to benzo[α]pyrene

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