Genetic Variation and Risk of Endometrial Cancer

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DECLARATION

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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Date

KATIE A. ASHTON
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ABSTRACT

Endometrial cancer is one of the most common female cancers in industrialized countries. Traditional risk factors associated with endometrial cancer are well understood and include excessive exposure to estrogen or estrogen unopposed by progesterone. However, variations in the genes that influence these hormones and their association with endometrial cancer have not been well investigated. By studying genetic variation in endometrial cancer, novel markers of risk may be discovered that can be used to identify women at high risk and for the implementation of specialised treatments. Polymorphisms in the genes involved in the following pathways; hormone biosynthesis, hormone receptors, estrogen metabolism, DNA repair and cell cycle control, have been suggested to be involved in the initiation and development of endometrial cancer. The focus of this study was to examine genetic variants in these pathways to assess the existence of an association with the risk of endometrial cancer.

In the first part of this study, the COMT V158M polymorphism was examined in a hereditary non-polyposis colorectal cancer (HNPCC) cohort to determine its association with disease expression. The heterozygous genotype was over-represented in women with endometrial/ovarian cancer that did not harbour mismatch repair (MMR) gene mutations. This result suggested that the COMT V158M polymorphism may alter the risk of developing HNPCC related endometrial/ovarian cancer in MMR mutation negative women. Since COMT is involved in the metabolism of estrogen and that estrogen is the main risk factor for endometrial cancer development, closer examination was warranted to determine the association of genetic variation involved in hormone-related pathways and endometrial cancer risk, outside of the context of an inherited predisposition to disease.

In the second part of this study, a cohort of 191 women with endometrial cancer and 291 healthy control women were genotyped for polymorphisms in genes involved in hormone biosynthesis, hormone receptors, estrogen metabolism, DNA repair and cell cycle control. The results revealed that variations in estrogen receptor alpha (ESR1) and beta (ESR2), and the androgen receptor (AR), were associated with an increase and decrease in endometrial cancer risk, respectively. Additionally, polymorphisms in CYP1A1, CYP1B1, GSTM1 and GSTP1 were related to a decrease in endometrial cancer risk. A trend was observed for the cyclin D1 870 G>A polymorphism and an increase in endometrial cancer risk, however, this result did not
reach significance. Taken together, these results revealed that perturbations in the hormone receptors and estrogen metabolism genes, may aid in the identification of women at high risk of developing endometrial cancer. Interestingly, stratification of the women with endometrial cancer revealed that combinations of polymorphisms in TP53 and MDM2 were associated with higher grades of cancer. This finding may possibly have significant implications as women with reduced apoptotic ability, due to combinations of polymorphisms in these genes, have an increased risk of presenting with higher grades of endometrial cancer, that are associated with lower survival rates.

In summary, the results of this thesis showed that variation in the estrogen and androgen receptors, and estrogen metabolism genes, may alter the risk of developing endometrial cancer. Moreover, polymorphisms in the cell cycle control genes, TP53 and MDM2, appear to be associated with higher grades of endometrial cancer. This study of polymorphisms may help explain genetic differences in individual susceptibility to endometrial cancer and are markers of risk that aid in the development of effective and personalised strategies to prevent disease development.

This study has improved the understanding of genetic variation associated with endometrial cancer risk. It has the potential to enhance our ability to treat women with endometrial cancer through improved identification and treatment strategies, by virtue of the genetic variation identified, that appears to predispose to disease.