MYOPIC RELATED RETINAL CHANGES AMONG THE HONG KONG CHINESE HIGH MYOPES

CHENG CHI KWAN

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CHENG CHI KWAN

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Certificate of Originality

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Mr. Cheng Chi Kwan (Name of student)

Abstract

Title of PhD thesis: **Myopic Related Retinal Changes among the Hong Kong Chinese High Myopes**

Mr Cheng Chi Kwan, PhD candidate

School of Optometry

Chief supervisor: Professor Carly S. Y. Lam

It has been often reported that sight threatening retinal complications are associated with high myopia more than -6 D in the adult population. High myopia is a leading cause of irreversible blindness, contributing around 6% to 13% of blindness as reported in previous worldwide studies.

In cities like Hong Kong where the prevalence of myopia is in the range of 70% to 80%; myopia starts as early as the start of schooling and progresses steadily throughout the schooling age. Prevalence of high myopia presents a threat to the visual quality of this population. There was little information on the early changes in the retina, as well as the consequence of high myopia among

schoolchildren and adolescents that would lead to retinal complications or other ocular pathologies.

This study aims to indentify the early changes in the retina among school children and adolescents with high myopia and whether these retinal changes are any different from those of the adult population. This information may help to identify the possible risk factors including biometric and demographic characteristics for children or adolescents having high myopia ocular complications in their later years.

In identifying an efficient and effective method in the detection of early retinal changes among the adolescent group, the latest available technology and instrumentation were explored. The Optomap was selected for the investigation of sensitivity and specificity in fundus screening.

To further understand on how the retina changes in a myopic bigger eye, as a result of myopia progression and axial elongation, retinal thickness variation along the horizontal meridian was also investigated. This may shed lights on the relationship between anatomical variations and retinal complications.

This study has three main objectives:

1. Identify an effective and efficient screening methodology
2. Determine the prevalence of retinal features for the 12 to 18 years high myopic adolescent and risk factors
3. Relate retinal thickness profile with the myopic retinal changes

1. Identify an effective and efficient screening methodology

To identify an efficient method in retinal screening / examination, the ultra wide field scanning laser ophthalmoscope was investigated. Fifty-four eyes identified with retinal / choroidal signs and eight normal eyes were recruited from 31 Hong Kong Chinese subjects to evaluate the use of Optomap on detecting retinal signs under non-mydriatic condition with standard procedure. Photodocumentation of fundal changes were taken by the Optomap under undilated conditions before a dilated fundus examination by a clinician. To combat the problem caused by the eyelid blocking the image, a cotton bud was used to retract the eyelid. Optomap images were evaluated by four other investigators for identifying retinal features under a masked condition. Results were compared with those obtained using a dilated fundus examination as the gold standard. The sensitivity and specificity of the Optomap averaged 76.4% and 71.9% respectively, which was similar to a

previous report by other researchers. The fundal signs commonly missed by all observers were lattice degeneration (2 cases), white-without-pressure (1 case), paramacular drusen (1 case), and pigmentary change (1 case). Paramacular drusen were detected by contrasting the red laser channel and green laser channel, while other missed fundal signs were located in the far peripheral retina apparently outside the field of the Optomap. The Optos non-mydriatic fundus imaging system offers high sensitivity and specificity in fundus screening. Using a cotton bud to retract eyelid may be a useful modification especially for droopy eyelid patients. Optomap has certain advantages; however, there are limitations especially in some areas of the peripheral fundus may not be accessible. As a screening tool, the Optomap permits fundus examination without the use of a mydriatic agent, which is more comfortable for the patients, and that a permanent digital record of the findings can be kept. However, the colours of the Optomap are the artificial combination of two laser channels, resulting in a distorted image. Retinal lesions at the outside edges of the retina might not be detected. The Optomap is a complementary method to the standard dilated fundus examination but not as a substitute, especially with a high myopic population with a high risk of having retinal lesions.

2. *Determine the prevalence of retinal features for the 12 to 18 years high myopic adolescent and risk factors*

To determine the prevalence and risk factors of myopic related retinal changes in young Hong Kong Chinese eyes with high myopia, 120 eyes were examined among school children with over -6 D myopia aged between 12 to 18 years. The eye with higher spherical equivalent error (SER) was used for analysis for each subject. Personal data collection, history related to myopia progression, biometry and documentation of retinal characteristics were performed with informed consent. Mean age of the subjects was 14.83 ± 1.58 years. Among the subjects, 50.8% were boys. The mean SER of the eyes was -8.41 ± 1.60 D. The five most frequent retinal lesions found were optic nerve crescents (52.5%), white-without-pressure (51.7%), lattice degeneration (5.8%) microcystoid degeneration (5%) and pigmentary degeneration (4.2%). Multiple logistic regressions showed axial length longer than 26.5 mm was a significant risk factor for peripheral lesions ($p = 0.008$, odd ratio 3.37), optic nerve crescents ($p = 0.019$, odd ratio 2.80) and white-without-pressure ($p = 0.017$, odd ratio 2.93). Peripheral retinal degenerative lesions and optic nerve crescent were found in a significant proportion of high myopic teenage subjects. There was a positive relationship between axial length and peripheral retinal lesions. There is a higher chance of

having retinal lesions in eyes with axial length exceeding 26.5 mm in the age between 12 - 18 years. Myopic related fundus changes could appear in early life in high myopic eyes.

3. Relate retinal thickness profile with the myopic retinal changes

The third study established the retinal thickness profiles in the central horizontal eighty degrees and relates retinal thickness profile with myopic retinal changes by comparing the profile between myopic and non-myopic eyes. The retinal thickness profiles of 30 myopic eyes (spherical equivalent error (SER) between -6.00 D and -13.63 D) and 31 non-myopic eyes (SER between +2.75 D and -0.50 D) were measured using the StratusOCT (Carl Zeiss Meditec, Dublin, CA). Two scan types were used: the Macular Thickness Map and the Customized Line Scan for a central 80 degrees horizontal retinal thickness profile. Myopic eyes have a thicker retina at the foveal center and fovea ($p = 0.002$ and 0.044 respectively), and thinner retina at other regions, compared to non-myopic eyes ($p < 0.01$, unpaired t-test). At other zones of the macula, the retina was significantly thinner in myopic eyes compared to non-myopic eyes ($p < 0.01$, unpaired t-test). From 40 degree nasal to 40 degree temporal retina, a general reduction of retinal thickness was observed across the myopic retina compared to the non-myopic

retina, except at 20 degrees nasal to fixation. The peripheral retinal thickness was approximately 7% thinner in myopic eyes compared to the non-myopic eyes.

General conclusions

Based on the results of the investigation with ultra wide field scanning laser ophthalmoscope, the Optos non-mydriatic fundus imaging system offers high sensitivity and specificity in fundus screening. The cotton bud eyelid retraction method may be a useful modification especially for droopy eyelid patients. However, there is still a chance that certain area of the fundus might not be identified. The Optomap is a complementary method to the standard dilated fundus examination but not a substitute, especially in a group with a high risk of retinal lesions, such as the high myopic population.

The results of this prevalence study point out that myopic related fundus changes could appear in early life in high myopic eyes. There was a positive relationship between axial length and peripheral retinal lesions. There is a higher chance of having retinal lesions in eyes with axial length exceeding 26.5 mm in the age between 12 - 18 years. As the myopic related retinal changes are present among this age group, though there are no urgent types of retinal lesion counted in our

study, lesions like lattice degeneration is a predisposing factor of retinal detachment. Thus the early detection and assessment of fundal changes among young high myopes is important.

An investigation of anatomatical retinal variation related to myopia, retinal thickness profiles have been established in the central horizontal eighty degrees in myopic and non-myopic eyes. This study found that myopic eyes have a thicker retina at the fovea and thinner retina at other regions compared to non-myopic eyes. From 40-degree nasal to 40-degree temporal retina, the peripheral retinal thickness was approximately 7% less in myopic eyes compared to the non-myopic eyes. We found retinal thickness reduction associates with high myopia in our study. There is a lot more to be done, such as correlating retinal changes with visual changes, and longitudinal monitoring to observe the changes over time.

List of publications and conference presentations

Publications:

Cheng, S. C. K., Yap, M. K. H., Goldschmidt, E., Swann, P. G., Ng, L. H. Y. and Lam, C. S. Y. (2008). Use of the Optomap with lid retraction and its sensitivity and specificity. *Clin Exp Optom* **91**, 373-378.

Cheng, S. C., Lam, C. S. and Yap, M. K.(2010). Retinal Thickness in Myopic and Non-myopic Eyes. *Ophthalmic Physiol Opt* **30**, 776-784.

Lam, C. S., Lam, C. H., Cheng, S. C. and Chan, L. Y. (2012). Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *Ophthalmic Physiol Opt* **32**, 17-24.

Conference Presentations:

Cheng, S. C., Lam, C. S. and Yap, M. K. Potential application of Optos Non-Mydriatic Widefield Imaging in photodocumentation and fundus screening. Presented at *The 15th Asia-Pacific Optometry Congress*, 2005, Tokyo

Cheng, S. C., Yap, M. K. and Lam, C. S. Measurement of peripheral retinal thickness using optical coherence tomography among Hong Kong Chinese myopes. Presented at the *11th International Myopia Conference*, 2006, Singapore.

Cheng, S. C., Ng, L. H., Lam, C. S., Goldschmidt, E. and Swann, P. G. Sensitivity and specificity of Optomap for fundus screening in a Hong Kong Chinese population. Presented at the *11th International Myopia Conference*, 2006, Singapore.

Cheng, S. C., Lam, C. S. and Yap, M. K. Eccentric retinal thickness in myopic and non-myopic eyes. Presented at *The 17th Asia-Pacific Optometry Congress*, 2009, Hong Kong

Cheng, S. C., Lam, C. S. and Yap, M. K. Prevalence and risk factors of myopic related retinal changes among Hong Kong Chinese teenagers with high myopia. Presented at *The 18th Asia-Pacific Optometry Congress*, 2011, Singapore

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I wish to dedicate this work to my mother Ms Cheng Wai Chun who would have been so proud to see the completion of my research thesis.

Cheng Chi Kwan

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1. Chapter One. Myopia

Among different types of refractive status, myopia draws the most attention in the literature. Myopia is defined as a refractive state in which parallel light rays entering an eye are focused in front of the retina when the eye is unaccommodated (Curtin, 1985). People suffering from myopia have blurry vision at distance, and need optical correction for distant vision.

The prevalence of myopia is much higher in Asian countries, including Hong Kong, Singapore and Taiwan (Edwards, 1999, Lam *et al.*, 1999, Wong *et al.*, 2000, Wu *et al.*, 2001, Fan *et al.*, 2004, Lin *et al.*, 2004, Quek *et al.*, 2004). The increase in prevalence of myopia in these areas has been even described as "epidemic" by some researchers (Grosvenor, 2003, Morgan *et al.*, 2004). The implication of myopia is not only the inconvenience in using optical correction, but also the possibility of ocular health problems leading to low vision (Yap *et al.*, 1990).

An increased prevalence of glaucoma has been found with increasing myopia, from 1.5% in those non-myopic and less than -1 D myopia to 4.2% in low

myopia (-1 D to -3 D), and 4.4% in moderate-to-high myopia (exceeded -3 D), which showed a twofold to threefold increased risk in myopic eyes as compared with non-myopic eyes (Mitchell *et al.*, 1999). This finding might also be independent to IOP reading (Grodum *et al.*, 2001). High myopic adult eyes are also reported to have higher risk of developing retinal pathologies, such as lattice degeneration, retinal breaks, retinal detachment, and myopic degeneration (Grosvenor and Goss, 1999, Tano, 2002, Lewis, 2003). Myopia leading to ocular complications is reported to be a major cause of legal blindness in many countries, e.g. China Japan, Israel, Italy, Scotland and the United States, (Ghafour *et al.*, 1983, Curtin, 1985, Tokoro, 1998, Avisar *et al.*, 2006, Cedrone *et al.*, 2006, Xu *et al.*, 2006). Therefore, the consequence of myopia may not only be a simple optical problem, but also a predisposition to complications such as its related changes and ocular pathologies.

1.1. Definition of myopia

Myopia is generally defined as a refractive state in which parallel light rays entering an eye are focused in front of the retina when the eye is not accommodated (Curtin, 1985). Some studies used -0.50D or more minus as the

criteria for counting myopia (Lin *et al.*, 2001, Wu *et al.*, 2001, Dandona *et al.*, 2002, Midelfart *et al.*, 2002, Murthy *et al.*, 2002, Saw *et al.*, 2002b, Nepal *et al.*, 2003, Shimizu *et al.*, 2003), while some others have used -0.25 D or more minus (Mavracanas *et al.*, 2000, Montes-Mico and Ferrer-Blasco, 2000), -0.75 D or more minus (Kleinstein *et al.*, 2003), or -1 D or more minus (Lithander, 1999). The most commonly used criteria of myopia among studies is -0.50 D or more minus. Such variations in the definition of myopia cause some misinterpretation when comparing different studies. It would be much better to have an agreed definition to avoid confusion and also make comparison of study easier. Other categorization of myopia would be discussed in the next Section.

1.2. Classification of myopia

Myopia has been classified according to the age of onset, degree of refractive error, the principle optical component and ocular health status. Table 1.2-1 summarizes the classifications according to the criteria used. The most commonly used classification was the one developed by Grosvenor (1987), which is based on the age that myopia was first identified or corrected. Under this system, myopia is classified as congenital (onset at birth), youth-onset (onset

at age ranged from 5 to late teens), early adult-onset (onset after physical maturity to age of 40), and late adult-onset (onset aged older than 40 years). The youth-onset myopia would probably be the type of myopia that draws most attention, since many studies showed significant increases in the prevalence of myopia during the period of school years (Lam and Goh, 1991, Goldschmidt, 1998, Edwards, 1999, Lin *et al.*, 2001), when compared with other age groups.

The classification according to the degree of refractive error was categorized as *low* (negative refractive error to –3 D), *moderate* (above -3 D and below -6 D), and *high* (>-6 D) (Curtin, 1985). This classification of myopia helps to identify the severity of the refractive condition; however, it could only give an impression on the numeric range of myopia.

The other type of classification refers to the principal optical component that correlated with myopia. Axial myopia is the type of myopia which refractive power increases due to elongation of the eyeball, which is the increase in axial length. On the other hand, refractive myopia is the increase in refractive power either by increased curvature or refractive index of cornea or lens. Most studies concluded that axial myopia was the main component for myopia development

and progression (Lam and Goh, 1991, Lo *et al.*, 1996, Lam *et al.*, 1999, Hyman *et al.*, 2005, Jorge *et al.*, 2007, Mutti *et al.*, 2007). The increase in vitreous depth was found to be the major component in contributing to the development of myopia (Lam *et al.*, 1999, Hyman *et al.*, 2005, Saw *et al.*, 2005a).

Another myopia classification refers to ocular health status. Duke-Elder (1970) defined pathologic myopia as a degenerative ocular complication, which is characterized by the presence of degenerative changes particularly in the posterior segment of the eye. Curtin (1985) stated that high myopia was often associated with excessive and progressive elongation of the globe, which resulted in degenerative fundus changes. Curtin also pointed out that physiologic (simple) myopia can progress to pathologic myopia, resulted from excessive axial elongation. A more current classification was described by Saw *et al.* (2005b); the type of myopia which accompanied by degenerative changes in the sclera, choroid, retina and associated with visual dysfunction described as “pathologic myopia”, “degenerative myopia” or “malignant myopia”.

Tokoro et al. (1998) defined pathological myopia as high myopia (i.e. -8.00 D or more) with visual dysfunction and stated that physiologic myopia should then be

categorized with normal corrected visual acuity and an absence of obvious fundus lesions associated with myopic degenerations.

Table 1.2-1 Classifications of myopia according to different criteria

Criteria for classification	Subcategories	Definitions
Age of onset	Congenital	Myopia onset at birth
	Youth-onset	Myopia onset from age of 5 years to late teens
	Early adult-onset	Myopia onset from late teens to age of 40 years
	Late adult-onset	Myopia onset after age of 40 years
Degree of Refractive error	Low	Negative refractive error from definition of myopia to -3 D
	Moderate	Myopia ranged from -3 D to -6 D
	High	Myopia more than -6 D
Principle optical component	Axial	Myopia which resulted from a failure of the refractive power from cornea and lens to compensate for the axial elongation
	Refractive	Myopia that resulted from the refractive power of cornea and lens outweighs the axial length of the globe
Ocular health status	Physiological	Myopia with normal visual acuity and absence of obvious fundus lesions associated with myopic degenerations, except small temporal crescents
	Pathological	Myopia accompanied by degenerative changes in the sclera, choroid, retina and associated with visual dysfunction

1.3. Prevalence of myopia

Definition of myopia varies from study to study and this may affect the presented prevalence. Studies of prevalence of myopia are mainly divided into cross-sectional and longitudinal observations, with considerations various factors including age, gender and ethnicity.

1.3.1. Myopia prevalence

Prevalence of myopia varied in different continents; in Asia can reach 70% to 90%, while in Europe 30% to 40%, and in Africa 10% to 20% (Saw *et al.*, 1996). Table 1.3-1 briefly summarizes the studies of prevalence of myopia worldwide in the last decade, listing the data according to the continent or region. The Table also shows the variation of methodology among studies, which affects the comparison of prevalence across studies, including cycloplegia and non-cycloplegia, subjective and objective refraction, and the difference in definition of myopia. Studies with cycloplegia were presumed to have lower prevalence as compared with non-cycloplegia as the concern of active accommodation during eye examination has been ruled out, and studies

incorporated objective and subjective refraction were believed to have better accuracy. When a more minus definition of myopia were used, the prevalence was also expected to be generally lower.

There are considerable differences in prevalence of myopia in schoolchildren at different places, from low prevalence of 1.2% in Nepal (Pokharel *et al.*, 2000) and 7.4% in India (Murthy *et al.*, 2002), to high of 81% in the 15 year-old Taiwan students (Lin *et al.*, 2001). This difference might be contributed by different ethnicity, and also affected by the general trend of increasing myopia prevalence with increasing age before reaching adulthood. There is a general phenomenon that prevalence of myopia was higher in East Asian countries such as Japan, Taiwan, Korea, Singapore and China and in developed countries, despite the difference in methodology and criteria adopted in their studies. The regional differences reflected on the ethnicity of the population. It has been suggested that there is possible genetic susceptibility among specific ethnic groups, such as the Chinese (Lam and Goh, 1991, Seet *et al.*, 2001). The prevalence of myopia shows significant differences among different ethnic groups. Asian children were more prone to be myopic than Middle Eastern and European Caucasian children (Quek *et al.*, 2004, Ip *et al.*, 2008a).

In East Asia, myopia is well above 50% of the population whereas in Europe, US prevalence is generally lower than 50%.

Table 1.3-1 Brief summary of prevalence of myopia studies worldwide (except Hong Kong)

Authors (year) [Sample location]	Methods for refractive error measurement	Sample	Age (years (yrs))	Number of subjects	Prevalence of myopia	Criteria for 1. refraction 2. myopia 3. others
Africa						
Naidoo *et al*. (2003) [South Africa]	Cycloplegic autorefraction	Population-based	5 - 15	4890	Myopia 3% - 4% in general 14 yrs: 6.3% 15 yrs: 9.6%	1. SER 2. ≦-0.5 D
Ayed *et al*. (2002) [Tunisia]	Health care screening		6 - 20	708	Myopia 9.1%	
Asia						
Lithander (1999) [Oman]	Vision screening and cycloplegic autorefraction followed by retinoscopy		6 and 12	6292	Myopia: 6 yrs: 0.56% 12 yrs: 5.16%	1. SER 2. ≦-1 D
Pokharel *et al*. (2000) [Nepal]	Cycloplegic retinoscopy and cycloplegic autorefraction	Non-selected	5 - 15	5067	Myopia 1.2%	1. SER 2. ≦-0.5 D 3. hyperopia ≦+2 D

Zhao *et al*. (2000) [China]	Cycloplegic retinoscopy and subjective refraction	Random sample	5 - 15	5884	Myopia: 5 yrs: absent 15 yrs: 36.7% (boys) 55.0% (girls)	
Lin *et al.* (2001) [Taiwan]	Cycloplegic refraction and autorefraction	Non-selected	7 - 18	10889	Myopia: 7 yrs: 20% 12 yrs: 61% 15 yrs: 81% 16-18 yrs: 84% High myopia >-6 D: 8.2% (girls) 6% (boys)	1. SER 2. ≦-0.5 D
Wu *et al*. (2001) [Singapore]	Non-cycloplegic autorefraction	Population-based	16 - 25	15095	Myopia: <-0.5 D: 79.3% <-6 D: 13.1%	2. <-0.5 D 3. only RE used
Dandona *et al*. (2002) [India]	Objective refraction; cycloplegia under or equal to 15 yrs, subjective over 15 yrs	Population-based	All ages	9882	Myopia: ≦15 yrs 3.19% >15 yrs 19.45% (≦15 yrs) ≦-3 D: 0.49%	1. SER (worse eye) 2. <-0.50 D 3. hyperopia >+0.50 D

					≦-5 D: 0.27% (>15 yrs) ≦-3 D: 9.14% ≦-5 D: 4.54%	
Murthy *et al*. (2002) [India]	Cycloplegic retinoscopy, cycloplegic autorefraction, and subjective refraction when VA ≦20/40	Random	5 - 15	6447	Myopia 7.4% Prevalence of myopia increase from 4.68% in 5 yrs to 10.8% in 15 yrs	1. SER 2. ≦-0.5 D 3. hyperopia ≦ +2 D
Saw *et al.* (2002a) [Indonesia]	Refraction and autorefraction	Population-based	21 or more	1043	Myopia ≦-0.5 D: 48.1% ≦-0.75 D: 36.9% ≦-1 D: 26.1%	1. SER
Saw *et al*. (2002b) [Singapore and China]	Cycloplegic autorefraction	Multi-center concurrent cohort study	7 - 9	671 from Singapore, 286 from Xiamen	Myopia: Singapore 36.7% Xiamen 18.5%	1. SER 2. ≦-0.5 D
Nepal *et al.* (2003) [Nepal]	Retinoscopy and subjective refraction (cycloplegia as supportive test)	Voluntary	5 - 16	1100	Myopia 4.3% No students more than -6 D	2. ≦-0.5 D

Shimizu *et al*. (2003) [Japan]	Autorefraction and subjective refraction	Population-based	40 - 79	2168	Myopia: 45.7% (men) 38.3% (women) Moderate myopia (-3 to -6 D) ~7.2% High myopia (>-6 D) ~0.5%	1. SER 2. ≦-0.5 D
Australia						
Attebo *et al*. (1999) [Australia]	Non-cycloplegic autorefraction and lensometry	Population-based	49 - 97	3654	Myopia 15%	1. SER 2. <-0.5 D
Wensor *et al*. (1999) [Australia]	Non-cycloplegic refraction and autorefraction	Population-based	40 - 98	4744	Myopia 17% 40-49 yrs: 23.6% 50-59 yrs: 16.3% 60-69 yrs: 12.4% 70-79 yrs: 11.9% ≥80 yrs: 16.8%	1. SER 2. <-0.5 D
Europe						
Wu *et al*. (1999) [Barbados]	Non-cycloplegic autorefraction (subject's habitual Rx for unreliable	Population-based	40 - 84	4709	Myopia 21.9%	1. SER 2. <-0.5 D 3. hyperopia

	autorefraction results)					>+0.5 D
Fledelius (2000) [Denmark]	Refractive information given by students and spot check; spectacle measurement and subjectively controlled (in doubtful case) (no cycloplegia)	Medical students	22 - 41	294	Myopia : 50% Myopia range -0.5 to -8 D (females) frequency 53.9% median -2.5 D median onset 16 yrs (male) frequency 45% median -1.5 D median onset 18 yrs	1. SER (spherical equivalent error) 2. ≦-0.50 D
Mavracanas *et al*. (2000) [Greece]	Questionnaires asking for ophthalmologist's prescription	Student population sample	15 - 18	1738	Myopia 36.8% 29.7% (male) 46.1% (female)	1. SER 2. <-0.25 D
Montes-Mico and Ferrer-Blasco (2000) [Spain]	Non-cycloplegic retinoscopy and subjective refraction; near retinoscopy for 3 year old children	Population sample of the Valencia Community	3 - 93	7621	Myopia 21.2% Myopia prevalence across age: 3-8 yrs: 2.5% 9-19 yrs: 25.7% 20-35 yrs: 30.1%	2. <-0.25 D 3. >+0.25 D

					36-45 yrs: 28.2% 46-65 yrs: 20.6% 66-93 yrs: 15.2%	
Villarreal *et al*. (2000) [Sweden]	Cycloplegia with 0.5% tropicamide and retinoscopy	Field study	12 - 13	1045	Myopia: 49.7% Bilateral myopia 39% High myopia (≦-5 D) : 2.5% in population, 5% in myopes	1. SER 2. ≦-0.5 D 3. Hyperopia ≦ +1 D 4. Astigmatism ≦-1.5 D
Midelfart *et al*. (2002) [Norway]	Non-cycloplegic autorefraction and subjective refraction	Population-based	20 - 45	3137	Myopia: 20-25 yrs: 35.0% 40-45 yrs: 30.3%	1. SER 2. ≦-0.5 D 3. ≦+0.5 D
Czepita *et al.* (2003) [Poland]	Cycloplegic retinoscopy		6 - 18	5023 students	Myopia 15%	
Middle East						
Rosner and Belkin (1991) [Israel]	From data of medical examinations	Nation-wide survey, non-selected	17 - 19	312,149	Myopia: 16.27% (bilateral) 1.69% (mono)	

North America						
Sperduto *et al*. (1983) [United States]	Visual acuity, pinhole test, lensometry, non-cycloplegic retinoscopy for poor visual acuity	Population-based	12 - 54	7401	Myopia 25%	1. SER 2. <0 D
Wang *et al*. (1994) [United States]	Non-cycloplegic autorefraction	Population-based	43 - 84	4926	Myopia 26.2%	2. <-0.5 D 3. hyperopia >+0.5 D
Kleinstein *et al*. (2003) [Multicenter study in 4 ethnic groups: African American, Asian, Hispanic, White)]	Cycloplegic autorefraction	CLEERE study	Asian 9.7 ± 2.11 African American 10.40 ± 2.50 Hispanic 10.20 ± 2.27 White 9.90 ± 2.30	2523 (534 African American, 491 Asian, 463 Hispanic, 1035 White)	Myopia: Overall: 9.2% Asian: 18.5% Hispanic: 13.2% African American: 6.6% White: 4.4%	1. SER 2. ≦-0.75 D 3. hyperopia ≦ +1.25 D

Villarreal *et al*. (2003) [Mexico]	Cycloplegia with 0.5% tropicamide and retinoscopy	Field study	12 - 13	1035	Myopia ≦-0.5 D: 44% ≦-5 D 1.4%	1. SER 2. ≦-0.5 D
Vitale *et al*. (2009) [United States]	Non-cycloplegic autorefraction	Population-based	12 - 54	9609	Myopia 41.6%	1. SER 2. <0 D
South America						
Maul *et al.* (2000) [Chile]	Cycloplegic autorefraction and subjective refraction	Population-based	5 - 15	5303	Myopia: 5 - 7 yrs: 3.5% 14 - 15years: 12.5%	1. SER 2. <-0.5 D
Schellini et al. (2009) [Brazil]	Cycloplegic refraction	Population-based	1 - 91	2454	Myopia: <10 yrs: 3.8% (lowest) 30 - 39 yrs: 29.7% (highest) ≥70 yrs: 21%	1. SER 2. <-0.5 D

1.3.2. Myopia prevalence in Hong Kong

The high prevalence of myopia among Hong Kong Chinese has been reported in several epidemiological studies by the Centre for Myopia Research at The Hong Kong Polytechnic University in the 90s (Edwards and Yap, 1990, Lam and Goh, 1991, Chan and Edwards, 1993, Edwards, 1999, Lam *et al.*, 1999).

For preschool ages, the prevalence of myopia was 2% in around 1996, and found to be increased to 6% in around 2006 (Fan *et al.*, 2011). A study among Hong Kong school children showed the prevalence of myopia (spherical equivalent refraction more than -0.50 D) increases from about 30% at age 6 - 7 years to about 50% in girls and 70% in boys at age 16 - 17 years (Lam and Goh, 1991). One decade later another study found that the prevalence of myopia increases from 17% at age before 7 years to 53% at age over 11 years (Fan *et al.*, 2004). The difference in prevalence might be affected by the different study methods. Fan *et al.* (2004) used cycloplegic refraction in their study while Lam and Goh (1991) used non-cycloplegic subjective refraction.

Another study of 1075 first-year university students with mean age 19.0 ± 0.9 years in The Chinese University of Hong Kong reported 91.7% students having myopia with mean refraction of -4.00 ± 2.64 D (Lo *et al.*, 1996). Goldschmidt and co-workers also examined 135 Hong Kong medical students in 1993 (cited by Goldschmidt (1998)), and found that the prevalence of myopia was 95.5%, with the average of degree of myopia was over -5 D. The prevalence of myopia was found to be 71% at the age from 19 - 39 years (Goh and Lam, 1994). However, prevalence of myopia was found to be lower in Hong Kong population over aged 40 (Lam *et al.*, 1994). In specific group of people, for example, with intensive near work related occupation, the prevalence of myopia may be even higher than the general population. Ting *et al.* (2004) examined a group of microscopists aged between 22 and 42 years, working in 8 hospital laboratories in Hong Kong and discovered that 95% of microscopists were myopic, with mean spherical equivalent error of -5.05 ± 3.16 D. It has been reported that myopia is more prevalent in some groups of people and probably is related to the nature of occupation that the person is engaged in. Similar finding has been reported in UK microscopists previously (McBrien and Adams, 1997).

Figure 1.3-1 briefly summarizes the prevalence of myopia among studies on different ages in Hong Kong general population during the 90s, the dotted line represents a shift of "2 decades" from the prevalence determined in those studies, and represents the actual situation of prevalence of myopia in the 2010s. A high prevalence of myopia is expected among the age group from 40 to 60 years, which was no so in the 90s.

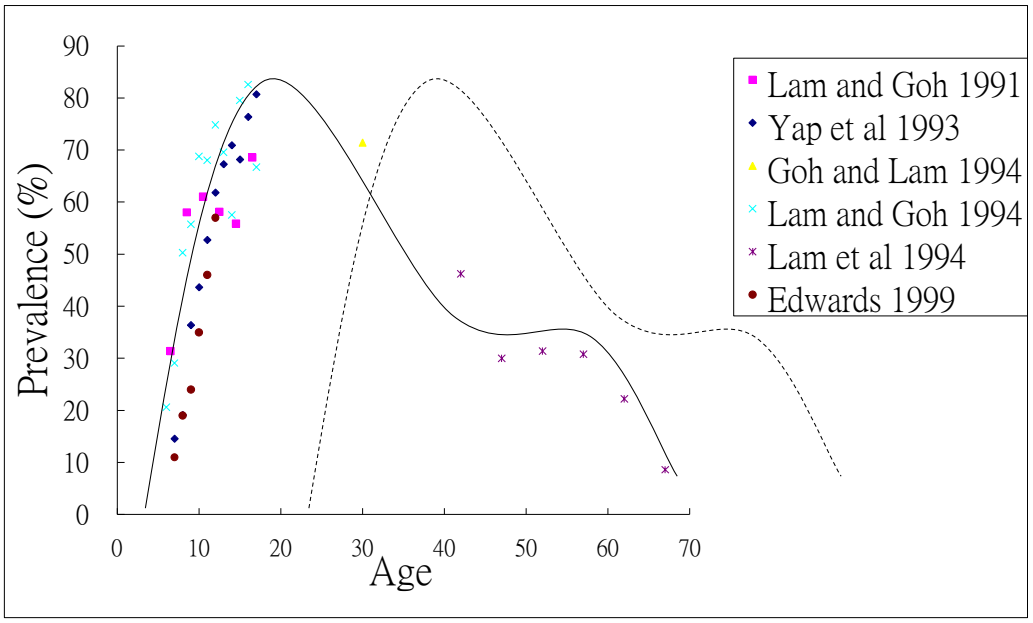


Figure 1.3-1 Prevalence of myopia in Hong Kong among different ages

1.3.3. Increased myopia with age

It is uncertain whether the prevalence of myopia tends to grow with age, as reported by Lin and colleagues (Lin *et al.*, 2001, Lin *et al.*, 2004), or is rather stable as the results found by Junghans and Crewther (2005) and by our research

group (Lam *et al.*, 2012). Lin *et al.* (2004) compared the data in Taiwan schoolchildren from 1983 to 2000, and found a significant increase in both the prevalence and the degree of myopia between study in 1983 and 2000 in Taiwan. The prevalence of myopia increased from 5.8% in 1983 to 21% in 2000 in 7 year-old children. At the age of 12, the prevalence of myopia has been increased from 36.7% in 1983 to 61% in 2000. An increase of myopia prevalence in 15-year-old children from 64.2% in 1983 to 81% in 2000 was also observed. The prevalence of high myopia over -6 D among 18-year-old students increased from 10.9% in 1983 to 21% in 2000. The mean myopia at the age of 12 years increased from -0.48 D in 1983 to -1.45 D in 2000, and from -1.49 D to -2.89 D for children aged 15. The authors suggested that the progressive increase in prevalence of myopia in Taiwanese schoolchildren over the 20 years may be due to increased near work activity. On the other hand, Junghans and Crewther (2005) compared their prevalence data in Australian children population in 1990s and 2000s and found no statistical significant difference in prevalence of myopia in 4 - 12 years schoolchildren, with average of 2.3% in 4 year olds and 14.7% in 12 year olds. It is inconclusive whether ethnicity plays the role in these different findings, or whether other factors such as schooling and living style play a part too instead. Apart from Junghans and Crewther (2005), there is evidence

showing that the prevalence of myopia increasing in Caucasian population in Australia and the United States. (Attebo *et al.*, 1999, Ivers *et al.*, 1999, Wensor *et al.*, 1999, Rose *et al.*, 2001, Junghans *et al.*, 2002, Lee *et al.*, 2002, Vitale *et al.*, 2009).

In Hong Kong, our research group found the prevalence of myopia in Hong Kong Chinese schoolchildren to be similar to the previously reported findings from nearly two decades ago (Lam *et al.*, 1999, Lam *et al.*, 2012). Myopia prevalence (>-0.50 D) was 18.3% at age of 6 and 61.5% at age of 12. The average refractive error was −0.06 ± 1.03 D at 6 years old and −1.67 ± 1.99 D at 12 years old. Prevalence of high myopia (>-6.00 D) was overall 1.8%, with an increase from 0.7% at the age of 6 to 3.8% at the age of 12 (Lam *et al.*, 2012). There is no evidence that the prevalence of myopia increased with time over the last two decades. There appeared a plateau effect on myopia prevalence. This may be in response to the introduction of intensive and early commencement of schooling, where children were raised in a competitive lifestyle environment, alongside urbanization during that period.

The rate of myopia progression was greatest between 6 to 10 years old (Lam *et al.*, 1999, Edwards, 1999). Hong Kong Chinese develop myopia at a young age, and myopia progression rate was quite steady throughout school years. It is expected that apart from the higher prevalence of myopia, with the mean spherical equivalent error of myopia with a progressing at a rate of about -0.32 D to -0.46 D per year, some children might be in the high myopia range, which exceeded -6 D, when they become adult. In Taiwan, Ho *et al.* (1994) reported that almost 24% of college student have myopia more than -6 D. Due to an increased aging progress of the present myopic population, it is concludable that the risk of eye pathology due to myopia may increase in the next half-century.

1.4. Aetiology of myopia

The mechanism of myopia development is still not well understood, but it is widely accepted that myopia is a multifactorial disorder (Curtin, 1985, Mutti *et al.*, 1996, Saw *et al.*, 1996, Morgan and Rose, 2005, Young *et al.*, 2007). Both genetic involvement and environmental factors contribute to the aetiology of myopia.

1.4.1. Genetics

Numerous studies revealed the hereditary characteristic of myopia. Familial correlation studies in school myopia pointed out that genetics played a role in myopia development, in which children with myopic parents were more likely to become myopic (Goss *et al.*, 1988, Mutti and Zadnik, 1995, Pacella *et al.*, 1999, Wu and Edwards, 1999, Guggenheim *et al.*, 2000, Rose *et al.*, 2002). Other studies showed that the refractive errors between monozygotic twins were more correlated than that between dizygotic twins (Goss and Wickham, 1995, Hammond *et al.*, 2001, Lyhne *et al.*, 2001). However, there may also be an environmental factor in these studies, as the children have similar living conditions as their parents.

Myopia can be inherited in monogenic mode or with complex traits. Some human genes have been found to be associated with myopia with Mendelian inheritance (Young *et al.*, 1998b, Young *et al.*, 1998a, Heath *et al.*, 2001, Naiglin *et al.*, 2002, Paluru *et al.*, 2003, Paluru *et al.*, 2005) and in gene polymorphism (Han *et al.*, 2006, Han *et al.*, 2009). Myopia was also found to be associated with systemic diseases and mutations including Marfan syndrome and Stickler

syndrome (O'Brien and Phillips, 2000, Logan *et al.*, 2004, Zejmo *et al.*, 2009b). Investigations on myopia and genetics reported that there were susceptible loci involving autosomal dominant, X-linked recessive, and also in complex mode of inheritance (Young, 2004, Hornbeak and Young, 2009).

1.4.2. Environmental factors

It is difficult to explain the rapid increase in prevalence of myopia in East Asian population by the explanation of genetic myopia (Goh and Lam, 1994, Lam *et al.*, 1994, Lin *et al.*, 2004). Lam and colleagues found the prevalence of myopia was 71% in population aged 19 - 39 years in Hong Kong, while the prevalence of myopia dropped to around 30% at age over 40 years (Figure 1.3-1)(Goh and Lam, 1994, Lam *et al.*, 1994). There are ample data on the strong relationship demonstrated between environmental factors and myopia progression, including higher education level (Wong *et al.*, 2002, Shimizu *et al.*, 2003, Quek *et al.*, 2004), better academic performance (Mutti *et al.*, 2002), increased near work and near work related occupation (Tan *et al.*, 2000, Mutti *et al.*, 2002, Ip *et al.*, 2008c) and more urbanized living area (Ip *et al.*, 2008b). On the other hand, engaging in

outdoor activities would reduce myopia progression (Rose *et al.*, 2008a, Rose *et al.*, 2008b, Dirani *et al.*, 2009).

1.4.3. Other proposed mechanisms

Current ideas on the aetiology of myopia also suggested that eye shape may cause relative hyperopic defocus on peripheral retina (Mutti *et al.*, 2000, Atchison *et al.*, 2004, Atchison *et al.*, 2005). With advances in peripheral refraction techniques (Fedtke *et al.*, 2009), further breakthrough on the understanding of the effect of eye shape could be expected. Also, the decoding process of optical signals and defocus of the eyes has become an interesting topic related to the mechanism of myopia (Smith and Hung, 1999, Tse *et al.*, 2007, Smith *et al.*, 2010). The application of dual-powered myopia control lenses has been successful in chick model, while it is yet to be confirmed in human eyes (Tse *et al.*, 2007).

Other studies also investigated the role of accommodation and the effect of near work versus outdoor activities in myopia development (Gwiazda *et al.*, 2003, Dirani *et al.*, 2009, Berntsen *et al.*, 2010, Low *et al.*, 2010). There appeared an

effect on myopic control using plus addition lenses for reading (Gwiazda *et al.*, 2003). Outdoor activities may protect children against myopia development (Dirani *et al.*, 2009). The authors proposed the effects of ultraviolet radiation exposure may partly explain the protective effect against myopia, the greater depth of field resulted from more constrict pupil under sunlight may play a role in the protective effect against myopia. They also hypothesized that there may be biochemical changes related to increased physical activity m have an inhibitory role on eye growth.

Investigation of myopia aetiology helps the design for myopia control methods. Current intervention of myopia progression involved genetic and environmental approaches, including genetic engineering (Hornbeak and Young, 2009, Stone and Khurana, 2010) or optical intervention (Gwiazda *et al.*, 2003, Cho *et al.*, 2005, Tse *et al.*, 2007).

2. Chapter Two. High myopia and its implication on ocular complications and visual performance

High myopia was usually defined as myopia -6 D or more (Curtin, 1985, Young *et al.*, 1998a, Gwiazda *et al.*, 2007), yet there were studies that included -5 D or more as high myopia (Vongphanit *et al.*, 2002, Logan *et al.*, 2004). Percival (1987) suggested a definition of high myopia as having an axial length of 26.5 mm or more, based on the increased prevalence of retinal detachment after cataract surgery. This definition was widely used in studies related to cataracts and high myopia (Fan *et al.*, 1999, Ku *et al.*, 2002, Tsai *et al.*, 2007).

The introduction of the concept of pathological myopia has raised concern about the ocular complications of high myopia, but it has been questioned for the level of severity of refractive error associated with specific pathology is not well documented. Duke-Elder (1970) defined pathologic myopia as a degenerative ocular complication, characterized by the presence of degenerative changes, particularly in the posterior segment of the eye. Curtin (1985) stated that high myopia was often associated with excessive and progressive elongation of the globe, which resulted in degenerative fundus changes. Curtin also pointed out

that physiologic (simple) myopia can progress to pathologic myopia as a result of excessive axial elongation. Tokoro (1998) presented the definition of "pathological myopia" which described myopia -4 D or more for children younger than 5 years, -6 D or more for children aged 6 to 8 years, and -8 D or more for aged over 8 years, with degenerations in posterior segment (Kobayashi *et al.*, 2005). Though the term pathological myopia has been used for so many years, the exact nature of the relationship between refractive error and ocular pathologies is still unknown (Saw, 2006).

There are certain types of ocular pathologies related to high myopia, for instance, myopic degeneration and posterior staphyloma. On the contrary, it is also possible to have high myopia without any ocular complications. Is there a demarcation of pathological and physiological high myopia? The current criterion for differentiating physiological and pathological myopia is the presence of degenerative changes in subjects with high myopia (exceeded -6 D or -8 D) (Zejmo *et al.*, 2009b). However, are there any other differences between the two groups in terms of genetics, age of onset, other associated disorders, visual performance and optical components?

2.1. Prevalence of high myopia

High myopia (myopia -6 D or more) is a health concern in the Chinese community due to its high prevalence (Wu *et al.*, 2001, Quek *et al.*, 2004, Wang *et al.*, 2009b) and its associated pathological complications (Saw *et al.*, 2005b). It has been reported that in young adult male Singaporean Chinese (14 - 19 yrs old) the prevalence of high myopia reached 6.6% of the population (Quek *et al.*, 2004). In Hong Kong, there was little information about the prevalence of high myopia in adolescents. The prevalence of high myopia among 5 - 16 year-old children was reported to be 1.19% (Fan *et al.*, 2004). Considering the average incidence of myopia of 11.8% in Hong Kong children between the age of 6 and 17 years of age (Lam *et al.*, 1999), and the averaged myopia progression of myopic Hong Kong children of approximately -0.50 D per year (Edwards, 1999, Lam *et al.*, 1999), it is expected that the prevalence of high myopia in adolescents should be greater in 12 - 18 year-old Hong Kong Chinese population. In Taiwan, an increasing trend of prevalence of high myopia in schoolchildren was reported (Lin *et al.*, 2004). In 12-year-old schoolchildren in Taiwan, the prevalence of high myopia increased from 0.2% in 1983 to 3.4% in 2000. In 18-year-old schoolchildren, the prevalence of high myopia increased from 10.9%

in 1983 to 21% in 2000. These prevalence data indicate that a large number of people in the Chinese population may develop high myopia associated complications, and this can seriously impact to our health service.

High myopia might be the result of physiological myopia progression in schoolchildren over time. According to Goss *et al.* (1987), the progression rate was -0.44 D per year in boys and -0.52 D per year in girls in optometric clinic samples. If primary education starts at 6 years of age, and incidence of schooling myopia occurs at that age in Hong Kong (Lam *et al.*, 1999), it is expected that a proportion of boys and girls might become highly myopic at the age of 20 and 18 respectively. The prevalence of high myopia reached 6.6% of the population in young adult male Singaporean Chinese (14 - 19 yrs old) (Quek *et al.*, 2004), while it was 1.19% among 5 - 16 year-old children in Hong Kong (Fan *et al.*, 2004).

2.2. Anatomical and physiological characteristics of the high myopic eye

Recent literature has reported some distinctive features related to highly myopic eyes. They include; optical component changes, changes in eye shape, retinal thickness variations and some common pathological manifestations. A better understanding on the development of these features will aid in the understanding of the pathological changes and visual performance of highly myopic eyes.

2.2.1. Optical components

Myopia progression is in fact a process of eyeball enlargement in axial myopia (Curtin, 1985). In high myopic eyes, there is an excessive increase in axial length and vitreous chamber depth as myopia progresses (Curtin, 1985), with axial length commonly found to be 26 mm or more. Carney *et al*. (1997) observed that high myopic eyes had steeper central corneal curvatures, deeper anterior and vitreous chambers, and longer axial lengths. They also revealed that corneal asphericity (Q) in high myopic eyes was significantly more positive than in low myopic and emmetropic eyes, which means a decreased peripheral corneal flattening was observed in high myopic eyes. There might be an increase in

crystalline lens thickness and curvature between myopic eyes and eyes with other refractive status (Lin *et al.*, 2001).

One of the definitions of high myopia was based on an axial length which equals or exceeds 26.5 mm, as it was found to be related to increased incidence of retinal detachment (Percival, 1987). Other studies examining cataracts and high myopia also used axial length 26 mm or more as defining high myopia (Fan *et al.*, 1999, Ku *et al.*, 2002, Tsai *et al.*, 2007). Gozum *et al.* (1997) reported the mean axial length among their 109 subjects was 28.3 ± 2.0 mm, with mean myopia of -12.3 ± 5.3 D. Tekiele and Semes (2002) examined 30 high myopic eyes with mean myopia of -8.1 ± 2.1 D found the mean axial length was 26.4 ± 1.1 mm.

In high myopic children, using the definition of -4 D or more myopia for children younger than 5 years, and -6 D or more myopia for children aged 6 - 8 years, Kobayashi *et al.* (2005) found that in a group of 80 high myopic eyes from 46 children (1 - 8 years old) the mean axial length was 25.7 ± 9.8 mm, with a mean refractive error of -8.4 ± 3.8 D. The large variation in axial length in high myopic children might imply that the cause of high myopia might not only be axial

elongation, but also some other congenital problem which could possibly affect other optical components, such as cornea. Unfortunately, there was no information on corneal curvature provided in this study.

Tekiele and Semes (2002) found the averaged corneal power of high myopic eyes was 44..07 ± 1.53 D in right eyes, and 44.10 ± 1.42 D in left eyes. These results seemed comparable to subjects having no high myopia. Zhang *et al.* (2011) found that when myopia increases the corneal asphericity coefficient (Q values) would be more oblate.

2.2.2. Eye shape

Atchison *et al*. (2004) measured the eye length, width and height for normal adult subjects including emmetropes and myopes up to -12.00 D with Magnetic Resonance Imaging (MRI). They revealed that myopic eyes were longer than the emmetropic eyes in all the three dimensions. Eye growth in myopic eye was greater in axial length than height, and at least for width (0.35 mm/D, 0.19 mm/D, and 0.10 mm/D, respectively). Atchison *et al*. tried to fit the eye shape with models of myopic growth (i.e. equatorial stretching, posterior pole

elongation, and global expansion) based on the linear dimensions of the eyes. They counted equatorial stretching and posterior pole elongation models as part of axial elongation model since it was impossible to differentiate the two models based on dimensions in their results. Considerable individual variations in dimensions of myopic eyes were reported, and neither global expansion nor the axial elongation model was enough to categorize all their samples. Only 25% and 29% of the eyes fitted global expansion and axial elongation models respectively, based on the height and axial length of the myopic eyes, and only 17% and 39% of the eyes fitted the global expansion and axial elongation models based on the width and axial length of the myopic eyes.

After publishing the analysis based on the linear dimensions of the myopic eyes (Atchison *et al.*, 2004), Atchison *et al*. (2005) further analyzed and compared eye shape and retinal shape of emmetropic and myopic eyes using the same group of data (Atchison *et al.*, 2004). They inferred the 3-D shape of the eye from the 3-mm-thick 2-D sections and performed mathematical ellipsoid fits on the retinal surface. Considerable variations were noted in the shapes of the ellipsoids among subjects with similar refractive error. In general, most of the emmetropic and myopic eyes were oblate, and the oblateness diminished with increased myopia.

The ellipsoid dimension increased with increasing myopia, in an approximate ratio of 3:2:1 for axial, height, and width dimensions, respectively. Only a small number of myopic eyes (12%) were prolate in shape and there were spread across the myopic range (from -1.00 D to -7.50 D). The ellipsoid fit test found that the ellipsoid vertices were generally rotated towards the nasal and above the ellipsoid centres. In myopic eyes, the ellipsoid centres were shifted 0.5 ± 0.4 mm nasal and 0.2 ± 0.5 mm inferior from the fovea, while the ellipsoids were tilted about the vertical axis by 11 ± 13 degrees. Atchison *et al*. also commented that the relative hyperopic shift measured for peripheral refraction was not due to prolate retinal shape, and that this point required further investigation.

2.2.3. Retinal thickness

Early investigations of retinal thickness in myopia were mainly focused on the macula region. Earlier studies using first and second generation OCT (optical coherence tomography) found that retinal thickness was not related with myopia (Lim *et al.*, 2005, Wakitani *et al.*, 2003). However, more recent studies using the Stratus OCT have reported that increasing axial myopia was associated with reduced macular thickness (Luo *et al.*, 2006, Lam *et al.*, 2007). Higher resolution

and a shorter scanning time of the newer OCT and a more detailed analysis of the data were offered as reasons to explain the new findings. Whereas the macula may be thinner in the myopic eye, it is unclear whether the peripheral retina of the myopic eye follows a similar pattern. Chujo *et al*. (1983) measured retinal thickness in five high myopic eyes (-8 D to -12 D) at the mid-posterior region between temporal equator and fovea using A-scan ultrasonography. They reported that retinal thickness was 116.2 ± 7.6 μm, and stated that it was thinner than those of the normal eye.

Apart from retinal thickness of the macular and optic disc areas, there seemed to be insufficient investigation of retinal thickness for other parts of retina. The idea of retinal stretching caused by increased myopia has been proposed long ago, and has been demonstrated in aniseikonia cases (Bradley *et al.*, 1983), visual acuity tests (Strang *et al.*, 1998) and psychophysical evidence (Chui *et al.*, 2005). From the results of retinal thickness investigation using OCT in central retina, it is believed that retinal stretching might anatomically take part in myopic eyes in central retina, but the effect and impact of retinal stretching on retinal thickness change is not clearly understood. Whereas the macula may be thinner in the myopic eye, it is unclear whether the peripheral retina of the myopic eye follows

a similar pattern. Further investigation is indicated for better understanding the retinal thickness profile in high myopic eyes.

2.2.4. Visual performance in high myopia

In high myopic eyes, visual performance is generally comparable to non-myopic eyes. However, visual performance could be reduced significantly when there is a pathological change in the high myopic eye. The anatomical differences may affect visual performance in high myopia.

Visual acuity of high myopic eyes deteriorates when pathological changes happen at the macula. Shih *et al*.(2006) investigated 552 high myopic patients aged 40 to over 70 years with a 10 year follow-up and reported that high myopic eyes with maculopathy tended to have poorer visual acuity and a poorer prognosis for visual acuity. High myopic eyes without maculopathy had an averaged visual acuity of 0.31 logMAR and 0.33 logMAR in initial and final examinations, respectively, showing a good prognosis for visual acuity. However, high myopic eyes with maculopathy had an averaged visual acuity of

0.57 logMAR and 0.94 logMAR in initial and final examination, revealing a poor prognosis for visual acuity after 10 years.

Contrast sensitivity in high myopic eyes without central retinal lesion were found to be comparable to low myopic eyes (Collins and Carney, 1990), despite the fact that spectacle correction would project a smaller retinal image size on the retina as compared with low myopic eyes. With contact lens correction, the contrast sensitivity of the high myopic eye was not significantly different from the low myopic eye.

Regarding the visual field sensitivity, Huang (1993) found that the degree of myopia and axial length showed a significant positive correlation with visual field total loss in high myopic eyes. Early functional changes appear in the tigroid fundus stage, and affected the upper temporal quadrant and 11-20 degrees annular area in visual field the most. This was independent of age and gender.

2.3. Risk factors in high myopia

High myopia might be driven by genetics or environment or both, causing gradual progression of myopia with years. Other systemic disorder might also relate to high myopia.

2.3.1. Genetics and environmental factors

High myopia was reported to be inherited in various patterns, including dominant, autosomal recessive and X-linked (Zejmo *et al.*, 2009a). Multiple myopia genetic loci have been identified, with at least 14 MYP loci approved by the Human Genome Organization Gene Nomenclature Committee (Hornbeak and Young, 2009). Some loci found to be responsible for high myopia were also related to the synthesis of certain types of collagen or sclera structural elements. This was proposed to be related with excessive elongation of axial length (Young, 2004, Morgan and Rose, 2005). Some gene mutations for X-linked pattern of high myopia were reported to be responsible for certain visual disorders (Paluru *et al.*, 2005). This genetic high myopia might be pathological, since vision disturbance was associated with it.

On the other hand, high myopia is not a homogenous ocular complication. There is evidence that high myopia might be the result of both genetic and environmental factors (Seet *et al.*, 2001, Morgan and Rose, 2005). It is possible that high myopia may be the result of myopia progression caused by environmental factor(s) interacting with a fairly normal genetic composition. This kind of genetic composition would not be expected to be pathological.

Pathological high myopia was reported to have a potential pathologic association with disorders such as microcornea, lenticonus anterior, congenital ectasia of the sclera, and mental impairment (Morgan, 2003). There is also a report that over 150 genetic diseases were associated with high myopia, including Marfan syndrome, Weill-Marchesani syndrome and Stickler's syndrome (Morgan and Rose, 2005, Zhang *et al.*, 2006). A significant proportion of children with high myopia in the age of 3 to 10 years in United Kingdom was also found to be associated with these systemic disorders (Logan *et al.*, 2004).

In the case of physiological high myopia, no associated complication is expected, but it is difficult to tell whether a high myopic eye may be predisposed to degenerative changes in later years.

2.4. Ocular complications associated with high myopia

Numerous reports pointed out that high myopia is associated with other ocular diseases, including: cataract (McCarty *et al.*, 1999, Lim *et al.*, 1999, Wong *et al.*, 2001), glaucoma (Wong *et al.*, 2003, Mitchell *et al.*, 1999, Daubs and Crick, 1981), chorioretinal abnormalities (Celorio and Pruett, 1991, Pierro *et al.*, 1992, Yura, 1998, Curtin and Karlin, 1971), and optic disc abnormalities (Tong *et al.*, 2004, Ramrattan *et al.*, 1999, Kobayashi *et al.*, 2005, Tekiele and Semes, 2002). The prevalence of glaucoma has been found to increase with increasing myopia, from 1.5% in non-myopes and less than -1 D myopia, to 4.2% in low myopia (-1 D to -3 D), and 4.4% in moderate-to-high myopia (exceeding -3 D), showing a twofold to threefold increased risk in myopic eyes as compared with non-myopic eyes (Mitchell *et al.*, 1999). This finding might also be independent of IOP readings (Grodum *et al.*, 2001). High myopic adult eyes are also reported to have a higher risk of developing retinal pathologies, such as lattice degeneration, retinal breaks, retinal detachment, and myopic degeneration (Grosvenor and Goss, 1999, Tano, 2002, Lewis, 2003). These myopia-related ocular complications can be a public health concern in a society like Hong Kong, where myopia is highly prevalent.

2.4.1. High Myopia-related retinal changes

Curtin (1985) summarized the common retinal features that could exist in myopic eyes, including posterior staphyloma, Fuch's spot, lacquer crack, choroidal sclerosis, peripapillary atrophy, chorioretinal degeneration, macular degeneration, subretinal neovascularisation, white-without pressure, pigmentary degeneration, pavingstone degeneration, lattice degeneration, retinal holes, and retinal detachment.

Retinal detachment is the major threat to vision in high myopic eyes, and lattice degeneration and white without pressure were suggested to be the risk factors (Swann and Schmid, 2002a). Retinal tears and detachment were found to be associated with moderate to high myopia (Grosvenor and Goss, 1999).

Most studies among Hong Kong children concluded that axial length elongation was the main cause for myopia progression (Lam and Goh, 1991, Lam *et al.*, 1999, Lo *et al.*, 1996). This axial elongation was found to be associated with increased prevalence of peripheral retinal changes in Western studies (Pierro *et*

al., 1992, Yura, 1998), such as white without pressure, lattice degeneration, pigmentary and paving-stone degeneration and retinal breaks.

In concluding Section 2.2 to Section 2.4, it is well understood that myopia may lead to ocular complications especially those with high myopia. There should be a more structured review on this topic and the aim of looking for effective and efficient means to identify subjects having ocular problems with high myopia and provide timely and appropriate treatment.

3. Chapter Three. Research gaps and the objectives of this study

As mentioned in previous sections, there is ample evidence concerning the ocular complications in high myopic eyes that can be sight threatening. In cities like Hong Kong where myopia starts early in life and progress steadily throughout the schooling age, there was little information about the impact of high myopia on retinal change in young adolescent population. There are many reports showing high myopia would cause a significant proportion of retinal changes and degenerations. However, the prevalence varies widely among different studies, even within the same ethnicity (i.e. Hong Kong-Chinese compared with Taiwan-Chinese). Also, to my best knowledge, there is no available information as to the prevalence of myopic related retinal changes associated with high myopia among the younger age group among the Chinese population.

3.1. High myopia in schooling age

As discussed in Section 2.1, the occurrence of high myopia can be congenital (before age of 5) or gradual. Therefore, further understanding of prevalence is crucial in order to know the impact of high myopia in schooling age children.

3.2. Ocular health assessment in high myopic children

Previous data showed retinal degeneration and retinal detachment could happen in paediatric high myopic eyes (Kobayashi *et al.*, 2005, Wang *et al.*, 2009a), Thus, the need for fundus examination for high myopic children is obvious. However, fundus examination with direct ophthalmoscopy with natural pupil is inadequate for high myopic eyes as many retinal anomalies including retinal holes, retinal breaks, snail track degenerations and lattice degenerations could exist asymptomatically at the peripheral retina (Lewis, 2003, Bec *et al.*, 1985a). Both the limited field of view of the fundus and the magnification of the view due to patient's refractive error would result in the possibility of overlooking those important fundal changes. The amount of magnification increases with increasing myopia, thus the magnification becomes particularly problematic in

high myopic eyes. Direct ophthalmoscopy does not provide stereoscopic view of the fundus and the examiner is forced to judge the observation based on monocular cues. Also, the illumination provided by direct ophthalmoscopy is badly affected by media opacities. Furthermore, when observing the peripheral retina, the field of view is significantly restricted by pupil size, and the view of the peripheral retina is distorted. (Semes, 1991, Friberg, 1994).

Binocular indirect ophthalmoscopy provides a wide view of the fundus and stereopsis. However, the examination requires dilation of pupil which resulting in patient discomfort and inconvenience like photophobia, reading difficulty and prohibition of driving. Routine dilated examination could provide early detection of peripheral retinal lesions. However, it might not be cost effective. Batchelder et al. (1997) assessed the benefits and cost of routine dilated examination for preventing vision-threatening peripheral retinal diseases in low risk patients in the northern California by a review of medical records for a 6 month period in 1992-1993. They estimated the cost would be as high as US$ 433,000 for each preventable case in low risk patients and they commented that routine dilated examination could not be effective in preventing most vision-threatening peripheral retinal pathologies. There is a need to find ways to bring cost down,

such as developing an effective screening method with low cost and high sensitivity and specificity.

3.3. How early is the manifestation of retinal changes?

Most studies concerning high myopia ocular complications focus on the general population (Curtin and Karlin, 1971, Kirker and McDonald, 1971, Celorio and Pruett, 1991, Pierro *et al.*, 1992, Lam *et al.*, 2005, Lai *et al.*, 2008). It has been reported that those ocular complications can happen in the early stage of life (Logan *et al.*, 2004, Kobayashi *et al.*, 2005). Logan *et al.* (2004) reported that a significant proportion of high myopic children were associated with ocular and systemic diseases, while retinal dystrophy was found in 7% of children aged 3 - 10 years. Kobayashi *et al.* (2005) found that mild chorioretinal atrophy around the optic disc is found in 16.3% highly myopic children aged 1 - 8 years. Compared with high myopic adults, ocular complications were relatively uncommon and mild in high myopic children, but still could be sight-threatening. There are reports that pointed out that high myopia is a major predisposing factor of paediatric retinal detachment (Chang *et al.*, 2005, Wang *et al.*, 2005, Wang *et al.*, 2009b).

3.4. Objectives of the study

This study has three main objectives:

1. *To identify an effective and efficient screening methodology*
2. *To determine the prevalence of retinal features for the 12 to 18 years high myopic group*
3. *To understand the anatomical variations in the high myopic retina*

Early detection of retinal changes and retinal detachment predisposing factors in young high myopic children would be beneficial to the prevention of sight threatening retinal detachment. Currently in Hong Kong optometric practice there is no standardized protocol for the clinical management for high myopia in young children. A cost-effective and high sensitivity and specificity retinal assessment, especially for those having high myopia is needed. There were little formal studies reported in journal articles on the performance of the ultra wide field scanning laser ophthalmoscopy. This is important to know the sensitivity and specificity of a wide field scanning laser ophthalmoscope in detecting retinal lesions.

On the prevalence of high myopia and its related complications, with modern technology, we might provide effective screening method for high myopic population and thus we can investigate on some of the characteristics of high myopic retinal changes. Further investigation in those characteristics might discover new risk factors of myopia related retinal changes and lead to a reform of ocular assessment in the early detection of asymptomatic sight threatening retinal problems and hence improves the prevention of high myopia related visual impairment.

In this study, the use of ultra wide field scanning laser ophthalmoscope for detecting retinal lesions would be investigated, and the prevalence of retinal changes in high myopic children eyes and their potential risk factors would be studied. The anatomical change in retinal thickness profile would be investigated, and comparison would be performed for the difference between high myopic eyes and non-myopic eyes.

4. Chapter Four. Evaluation of screening method for fundus examination

This study has been published in 2008:

Cheng, S. C. K., Yap, M. K. H., Goldschmidt, E., Swann, P. G., Ng, L. H. Y. and Lam, C. S. Y. (2008). Use of the Optomap with lid retraction and its sensitivity and specificity. *Clin Exp Optom* **91**, 373-378.

4.1. Introduction

Retinal detachment is a major threat to vision, and some peripheral retinal degenerations are major predisposing factors (Byer, 1979, Bec *et al.*, 1985b, Swann and Schmid, 2002b, Lewis, 2003). Many retinal anomalies including retinal holes, retinal breaks and retinal degeneration (e.g. lattice degeneration) can exist asymptomatically at the peripheral retina (Bec *et al.*, 1985b, Lewis, 2003). Clinically, peripheral retinal degenerations are detected by dilated fundus examination using binocular indirect ophthalmoscopy (BIO). Routine dilated examinations can provide early detection of peripheral retinal lesions. However, it might not be cost effective.

Batchelder *et al*, (1997) assessed the cost-effectiveness of a routine dilated examination for preventing vision-threatening peripheral retinal diseases in low risk patients (i.e. subjects without prior eye disease or surgery in posterior segment, no history of trauma and diabetes, not high myopia of >-6 D) in northern California using a review of medical records those patients aged 20 or older in the 6-month period from October 1992 to March 1993 and found routine dilation may not be cost effective in low risk patients (i.e. no known retinal disease or risk factors, myopia less than -6 D, no diabetes and no prior anterior eye surgery, and no previous trauma involved posterior segment). Dilated fundus examination for 265,783 patients only detected 38 patients to have retinal problems at most. Pollack and Brodie (1998) also investigated the diagnostic yield of routine dilated fundus examinations by reviewing 1,094 records in patients with normal vision, with a refractive error not greater than 3.00 dioptres of myopia and without risk factors for retinal disease. They estimated that the rate of detection of clinically significant fundus problems, such as choroidal naevus and preretinal fibrosis, through routine dilated fundus examination in those patients was 2.73%. These two studies pointed out that although routine dilated fundus examination is beneficial in detecting peripheral lesions, even among patients without risk factors of retinal problem but per positive case, it is

an extremely expensive procedure. Moreover, the associated pupil dilation results in some temporary patient discomfort and inconvenience such as photophobia, reading difficulty and the prohibition of driving. This raised the need of an effective and efficient fundus screening method which may be more cost-effective.

Apart from using BIO as the conventional method of fundus assessment, now we have the scanning laser ophthalmoscope for examining retina and even peripheral retina. Scanning laser ophthalmoscopes were first introduced to image the retina using a laser by Webb *et al.* (1980). Scanning laser ophthalmoscopes may have either a spherical or an ellipsoidal mirror to focus the laser beam on the patient's retina. Instruments with a spherical focusing mirror are called as "conventional retinal scanners based on scanning laser ophthalmoscopy". Those using ellipsoidal focusing mirror can be called as "wide field scanning laser ophthalmoscopy". The conventional retinal scanners with spherical mirror obtain a less distorted image, as they use a standard scanning geometry. They only obtain central fundal image within the central 40 degree (Berendschot *et al.*, 2003, Anderson *et al.*, 1998, Friberg *et al.*, 2003). The ultra wide field scanning laser ophthalmoscope with ellipsoidal mirror has been introduced since 1998 for

providing a more cost-effective peripheral fundus evaluation. The laser scanning ophthalmoscope enables quick screening of the retina up to 200 degree.

Optomap (Panoramic200; Optos, Marlborough MA, US) is the only one ultra wide field scanning laser ophthalmoscope commercialized for clinical use. Optomap has been claimed to provide non-mydriatic digital fundus photography up to 200 degree field of view (Optos, 2001). It incorporates an ultra-wide field ellipsoidal mirror, with a red (633 nm) and a green (532 nm) low powered laser scanning in two dimensions over the retina. A digital image of 2000 x 2000 pixel is formed for each shot. The duration of capture is 0.25 second which is much less time consuming when compared with the duration of a dilated fundus examination. The images obtained through non-dilated pupil from red and green laser can be displayed separately, which can separate the images from outer retina and choroid. This is particularly useful in identifying subtle changes in outer retina and choroid leading to a better understanding of the relationship between retinal degeneration and visual defects. This instrument might offer a sensitive and specific fundus screening in this study.

4.1.1. Previous studies on ultra wide field scanning laser ophthalmoscope

There are few studies reporting high sensitivities in picking up retinal pathologies by Optomap. Friberg *et al.* (2003) examined the sensitivity and specificity of Optomap using 124 Optomap images reviewed by two retinal specialists. In their study, a technician recorded the Optomap images for their subjects before visiting the retinal specialists. The Optomap images were captured by the same technician under ambient office-light conditions. The retinal specialists did not know whether their patients has undergone imaging or not, they performed dilated fundus examination using binocular indirect ophthalmoscopy and slit-lamp biomicroscopy with 20 D and 78 D lens respectively, on the subjects. They documented the results in the clinical chart and decided if there is any follow-up required. The Optomap images were then reviewed by the same retinal specialists under masked condition (after at least 3 months since the patients' visit) to give diagnoses and suggested the follow-up visit intervals. They reported the sensitivities were 74% and 78% for two retinal specialists and the specificities were 78% and 74%, respectively. Also, 82% of their follow-up recommendations based on Optomap images were in agreement with their dilated fundus examinations. However, most of the patients (i.e. 86

cases out of total 124 Optomap images) had rather central fundus problem, including diabetic retinopathy, central retinal vein occlusion, retinal toxoplasmosis, retinal macroaneurysm, branch retinal artery occlusion, age-related macular degeneration, macular edema, and neovascularization of the disc.

Other studies have also reported Optos has high sensitivities and specificities. Puliafito and Baumal (2000) examined 86 eyes in 45 patients and reported that the sensitivity and specificity of Optomap is 95.8% and 100% respectively in detecting retinal pathologies. Pandya *et al.* (2002) recruited two retinal specialists to make diagnoses and give management suggestions on Optomap images extracted from 50 patients in a masked manner. The sensitivities in their study were 90% and 73%, respectively for the two specialists. Escalona-Benz *et al.* (2003) found a significant correlation between Optomap with standard dilated fundus photography and B-scan echography in the detection of posterior segment tumours. Nath *et al*. (2005) compared the Optomap with slit lamp ophthalmoscopy with a fundus lens and binocular indirect ophthalmoscopy by examining 50 consecutive patients with known or suspected retinal lesions. They revealed that they would miss retinal lesion in 13 eyes (26%) if they performed

the review of Optomap only without the dilated fundus examination. However, these reports lacked details as to methodologies, and focused on pathological changes in the central fundus. So it is difficult to compare the results of these studies without a standardized methodology. A further investigation with a standardized method and analysis is indicated, and the ability of Optomap in studying peripheral retina should be investigated.

Revelli *et al.* (2005a) introduced a new clinical modification of Optomap acquisition called Steered Exam. In Steered Exam, subjects' retina were imaged using the Optos instrument fixating at 15 degree eccentrically at 12, 3, 6, and 9 o'clock positions with a minimum 5 mm pupil, hence images could be captured at the far periphery of the retina. Revelli *et al*. carried out a multi-center, open, non-randomized trial on 403 subjects (mean age 38.91 years, ranged from 18 - 82 years) recruited from three optometric clinics. The study has setup a "gold standard" for the observation of the retinal examination by having a referee examiner who was informed of patients' previous examination results and who had performed the dilated fundus examination utilizing binocular indirect ophthalmoscope (BIO), and re-evaluated the Optomap images. Revelli *et al.* compared both the Standard, the Steered Exam of Optomap and fundus

examination by BIO with the “gold standard” in detecting clinically important retinal findings. They discovered that Steered Exam and BIO examination of retina both had the sensitivities of 84.28% for anterior retinal findings (equator to ora serrata), and 86.12% for posterior retinal findings (posterior pole to equator) when compared with the “gold standard” (i.e. prior diagnosis + BIO + Optomap). High specificities were also obtained by the Steered and BIO exam, having both 98.02% for anterior retinal findings and 94.70% for posterior retinal findings. They commented that both the Standard examination by Optomap and the BIO examination of fundus failed to observe a small but significant percentage of retinal findings when compared with the “gold standard”. Based on the reason that the types of missed retinal findings were different between the Optomap exam and the BIO exam, they suggested the combination of Optomap exam and BIO exam would improve the detection of retinal abnormalities. Unfortunately, there was a lack of further details on the design of the Steered exam, we do not know how the new fixation targets guides the subject to look at the specific areas stably. If the fixation target was positioned on the inside of the instrument, the subject would probably accommodate causing pupil constriction, and making a 5 mm undilated pupil size nearly impossible. Therefore, further investigation should be performed on the “Steered exam” mentioned.

4.2. Objectives and methodology

This study was to evaluate a screening method for fundus examination, by the investigation of the sensitivity and specificity as the measuring outcomes. The Optomap was investigated under non-mydriatic condition with standard procedure and eyelid retraction.

Fifty-four eyes identified with retinal/ choroidal signs and eight normal eyes were recruited from 31 Hong Kong Chinese subjects from the Hong Kong Polytechnic University Optometry Clinic, with age ranged from 13 to 81 years. Our study followed the tenets of the Declaration of Helsinki and was approved by the Human Subjects Ethics Sub-committee of The Hong Kong Polytechnic University. Informed consent was obtained from all subjects.

Photo-documentation of the fundal changes was taken with the Optomap under undilated pupil conditions before a dilated fundus examination. All Optomap images were acquired by a clinician under standard procedures and all dilated fundus examinations were performed by another clinician utilising binocular indirect ophthalmoscopy and slit lamp biomicroscopy with a fundus lens.

Optomap images were evaluated by four investigators to identify retinal features

under masked condition. Image contrast and exposure levels of the red and green colour channels could be adjusted manually or optimised automatically by its software. All results were matched with the International Classification of Disease, Ninth Revision (ICD-9-CM) for each type of retinal feature and recorded on a predesigned form. Results from BIO and slit lamp biomicroscopy with a fundus lens were used as the reference for comparison with Optomap data.

4.2.1. Equipment

Optomap consists of an alignment system and a capturing system. In the alignment system, positioning of the eye can be achieved either by the patient or the operator (Optos, 2001). The fixation pattern is a green spot light with a surrounding red ring. The brightness of the fixation pattern can be set to three different level of luminance (Dim, Medium, and Bright) in the Optomap software for patients with different level of media clarity. When the red ring is thin but still complete and the green circle is centered within the ring, the patient's eye is in correct position. The alignment can also be monitored in real time by the operator through an infrared patient camera. A correct alignment is that the patient's iris fills the eye position overlay circle in the patient camera image

window. This enables the operator to guide the patient to the correct position despite of the difficulties patient encountered in fixation or alignment.

The Optomap incorporates a new development of scanning laser ophthalmoscopy for the capturing system. It uses an aspheric, ellipsoidal mirror as the retro-scanning mirror of the scanning laser ophthalmoscope which provide wider scanning field (200 degree) as compared with older system (approximately 40 degree)(Optos, 2001). It has been noted that the aspheric mirror optimizes the optical path length which reduces the aberrations inherent in spherical mirrors utilized in conventional scanning laser ophthalmoscopes (Friberg *et al.*, 2003, Anderson *et al.*, 1998). The aspherical ellipsoidal mirror also allows the scanned beam across the mirror surface to compensate for the natural astigmatism of the eye at the wider angles of view (Anderson *et al.*, 1998). The field of view of the scanning laser ophthalmoscope is improved by the increased size of the mirror resulting in a large scanning angle imaging 200 degree of the fundus, which is panoramic when compared with the conventional scanning laser ophthalmoscope, that having not more than 40 degree scanning angle (Friberg *et al.*, 2003, Berendschot *et al.*, 2003, Anderson *et al.*, 1998).

The ellipsoidal mirror has two foci. When the incident laser beam composed of wavelength 633 nm (red) and 532 nm (green) is introduced to the mirror through one focus (“real point of scan”), the beam always passes through the second focus (“virtual point of scan”) for directing the scanned illumination beam within the eye, and reflected back at the same path. Since the laser beam scans through the real point, the retina is to be covered by the scanning beam in two dimensions. (Optos, 2001)

4.2.2. Optomap Image acquisition

All Optomap Image acquisitions were carried out by the same examiner (SC). The Optomap images were taken with the Optos Panoramic 200 system (Optos plc, United Kingdom) under non-dilated condition in a dim environment. Subjects looked into the instrument with one eye and adjusted their eye position in order to see the fixation pattern. The clinician could check the patient's eye position and guide the patient to the correct position and vertex distance. Since eyelashes and lids may cover some part of the images, two to five images of each eye were used to identify retinal features in order to obtain the maximum field of view using standard procedures. To combat the problem of the eyelid blocking the image, eyelid retraction utilizing a cotton bud was applied when necessary (Figure 4.2-1).

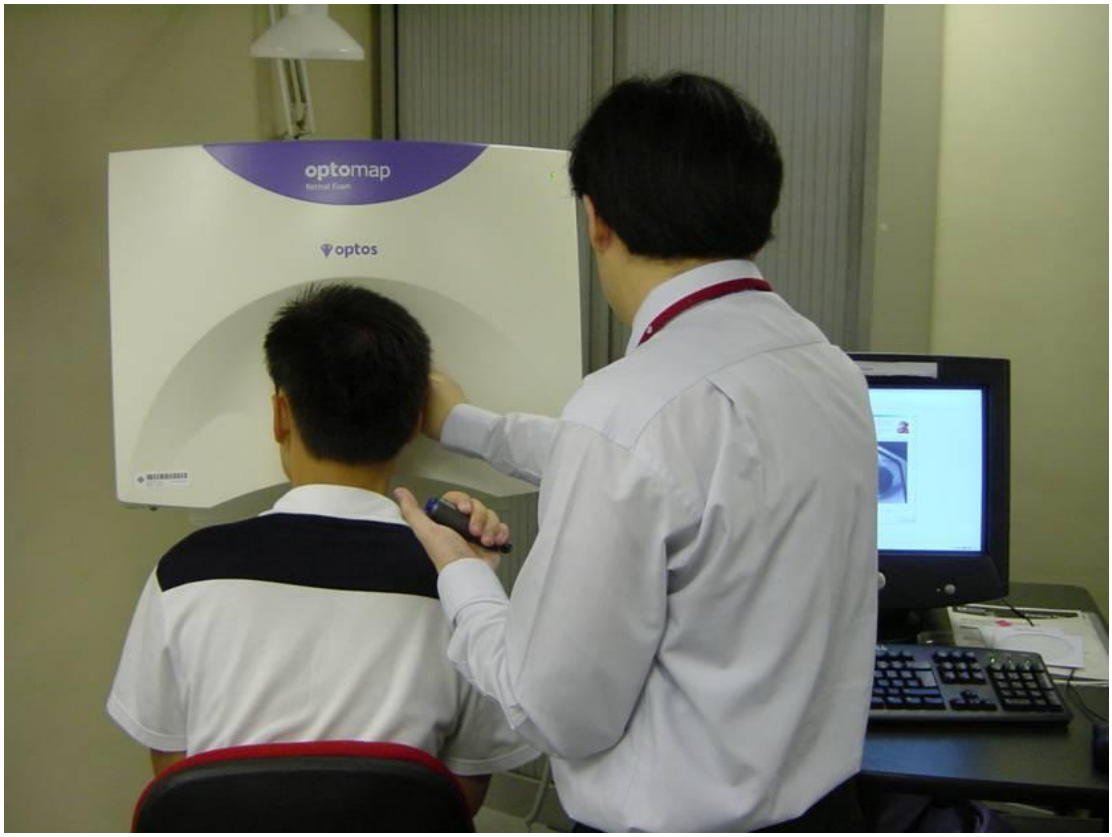
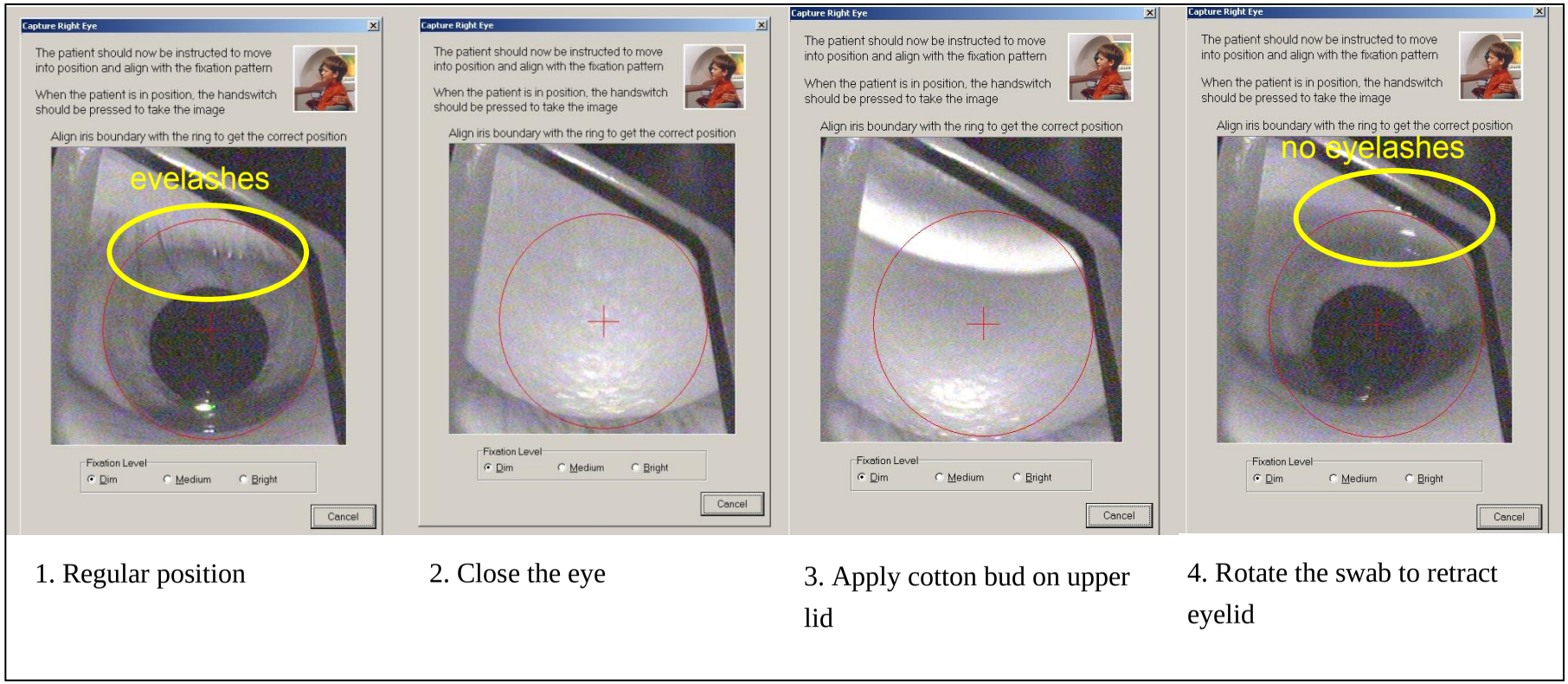


Figure 4.2-1 Optomap Image acquisition

4.2.3. Eyelid retraction during Optomap acquisition

Eyelid retraction was performed by cotton wool bud for those images blocked by the eyelid or eyelashes, with the help of real time fixation alignment - monitored on the computer monitor. The subject aligned to the fixation pattern and closed his eye. Then the cotton wool bud was applied to the upper lid. The swab was rotated to retract the eyelid. The eyelashes shown on the computer screen were removed from the field of view (Figure 4.2-2).

Imperfection of images caused by eyelashes can be solved by eyelid retraction. Figure 4.2-3 shows the comparison of an Optomap picture with and without eyelid retraction. With eyelid retraction, the temporal retina could be observed and also laser scars at the periphery.



1. Regular position

2. Close the eye

3. Apply cotton bud on upper lid

4. Rotate the swab to retract eyelid

Figure 4.2-2 Eyelid retraction procedure

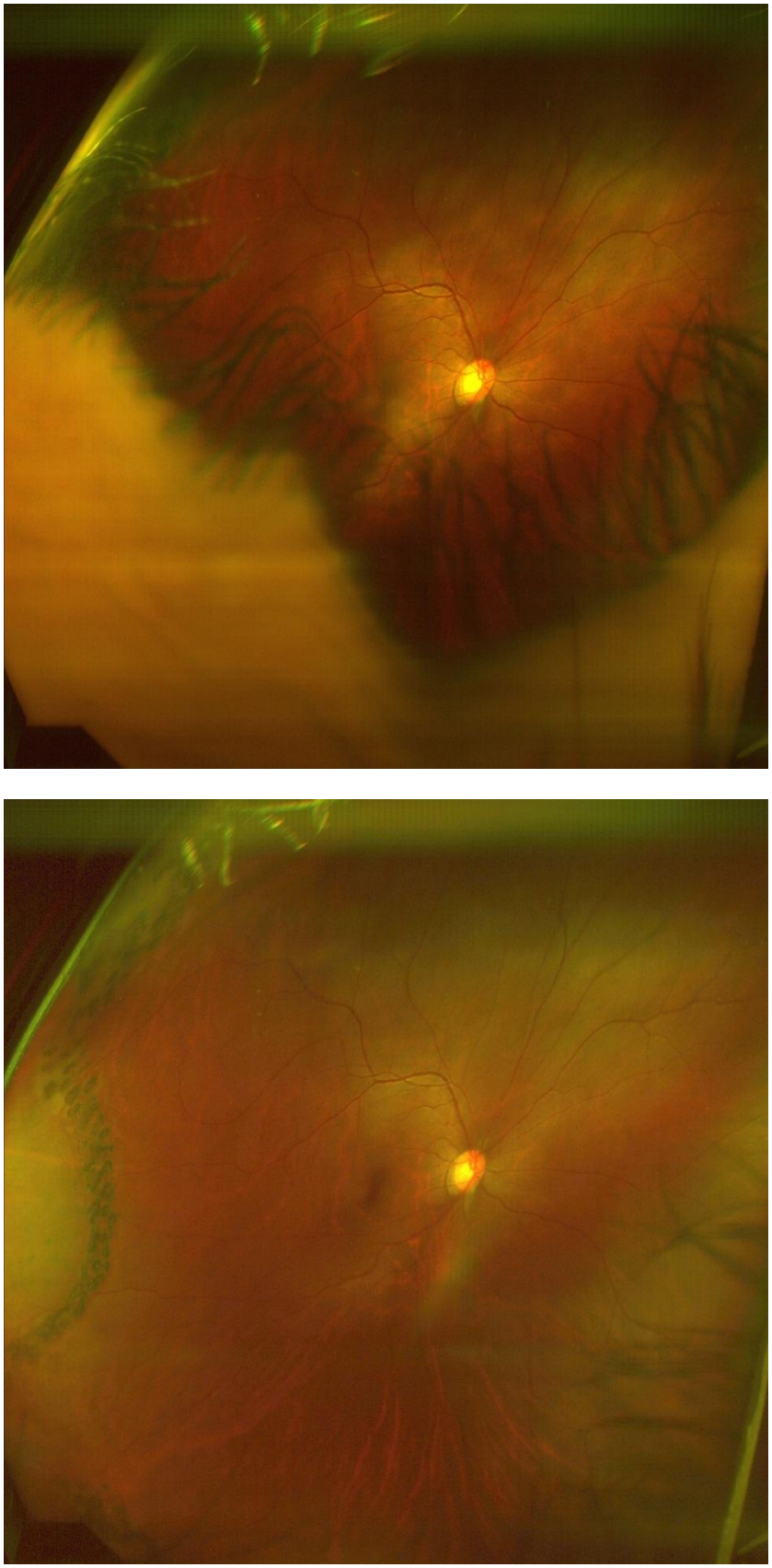


Figure 4.2-3 Comparison of an Optomap with (top) and without (bottom) eyelid retraction in a case.

4.2.4. Contrast enhancement by adjustment of the colour channels

No contrast enhancement was done during the Optomap image acquisition. Contrast enhancements were done by the Optomap observers during the identification of retinal features in the Optomap. Those enhancements included contrast adjustment in red and green channels, and also adjustment in gamma channel. All observers familiarized themselves with the contrast enhancement technique before the identification of retinal features in Optomap.

Different retinal abnormalities at different retinal layers can be picked up by the two light sources of Optomap. The green channel can highlight retinal haemorrhages at inner retina (Figure 4.2-4), the red channel can pick up retinal features like choroidal naevus (Figure 4.2-5). Floaters could be differentiated by taking pictures at different times and observing their change of position. Since a floater was in front of the retina it cast a shadow onto the retina and the shadow could be observed in both the red and green channels (Figure 4.2-6). By viewing the pictures in the red and green colour mode, we could differentiate in which layer the feature was located.

Figure 4.2-4 Appearance of retinal haemorrhage in Optomap: (left) Red-green composite image; (middle) Red channel (Choroidal layer); (right) Green channel (Inner retinal layer)

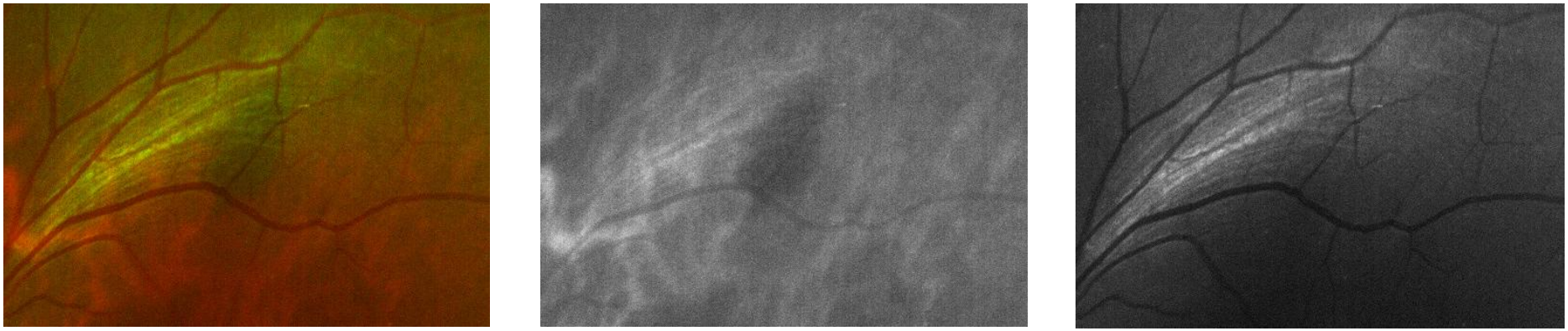


Figure 4.2-5 Appearance of choroidal naevus in Optomap: (left) Red-green composite image; (middle) Red channel (Choroidal layer); (right) Green channel (Inner retinal layer)

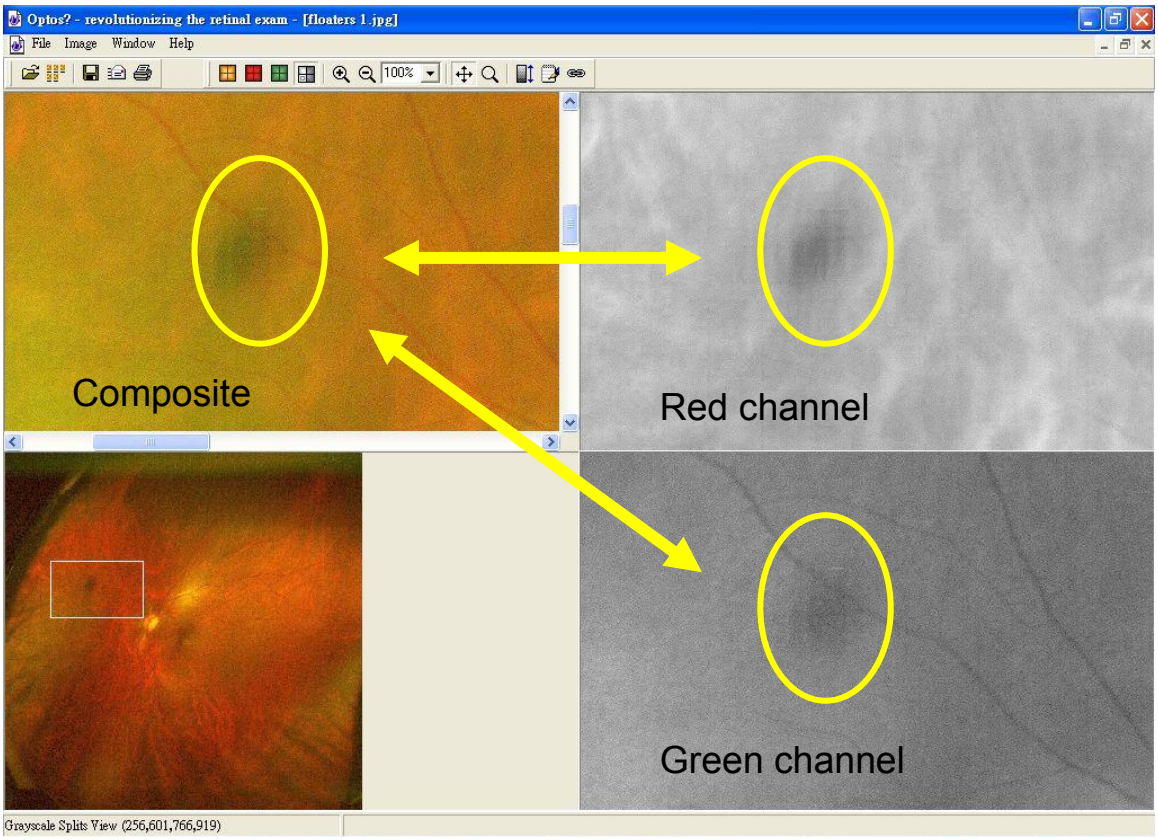


Figure 4.2-6 Floater which is shown in the Optos U-Revu software

4.2.5. Fundus examination by BIO

Dilated fundus examinations were performed by another investigator using BIO, following pupil dilation with Tropicamide 1.0%, and recorded on a pre-designed form. Dilated pupil sizes were not less than 7 millimetres in diameter. Results were matched with the international classification of disease ninth version (ICD-9-CM) for each type of retinal feature. Digital images were recorded either by indirect ophthalmoscopy with a video output, the digital fundus camera, or slit

lamp biomicroscopy. If image recording was impossible, then the retinal signs were observed by two optometrists.

4.2.6. Classifications of retinal features

Table 4.2-1 shows the frequencies and types of retinal features which were classified under the ICD-9-CM revealed by BIO. The retinal features were mainly white-without-pressure (WWOP) (as "Peripheral retinal degeneration, unspecified"), lattice degeneration, circumpapillary dystrophy of the choroid, peripheral scars and vitreous degeneration. There were 142 retinal features found in the BIO examinations. About half of the retinal features were located beyond equator. Among the 62 cases, 13% has no retinal abnormality detected, 42% showed peripheral retinal signs only, and 45% showed macular and optic disc problems (Figure 4.2-7).

Table 4.2-1 Frequency of fundus signs in 62 eyes under the International Classification of Diseases, Clinical Modification (ICD-9-CM)

Frequency of fundus signs in 62 eyes under the International Classification of Diseases, Clinical Modification (ICD-9-CM)	
Peripheral retinal degeneration, unspecified	24
Lattice degeneration	14
Circumpapillary dystrophy of choroid, partial	13
Peripheral scars	11
Vitreous degeneration	11
Round hole of retina without detachment	7
Nonexudative senile macular degeneration	6
Macular degeneration (senile), unspecified	5
Drusen (degenerative) (Macular and post pole)	5
Microcystoid degeneration	5
Vitreous membranes and strands	5
Pigmentary retinal dystrophy (e.g. RP)	4
Old detachment, partial	3
Paving stone degeneration	3
Dystrophies primarily involving Bruch's membrane	3
Chorioretinal scars (post- inflammatory/ surgical / traumatic)	3
Chorioretinal scar, unspecified	3
Other macular scars	3
Retinal defect, unspecified	2
Other scars of posterior pole	2
Optic atrophy associated with retinal dystrophies	2
Choroidal nevus	1
Macular cyst, hole, or pseudohole	1
Macular puckering	1
Retinal hemorrhage	1
Retinal exudates and deposits	1
Retinal edema	1
Retinal ischemia	1
Vitreous floaters	1
Total retinal features identified	142

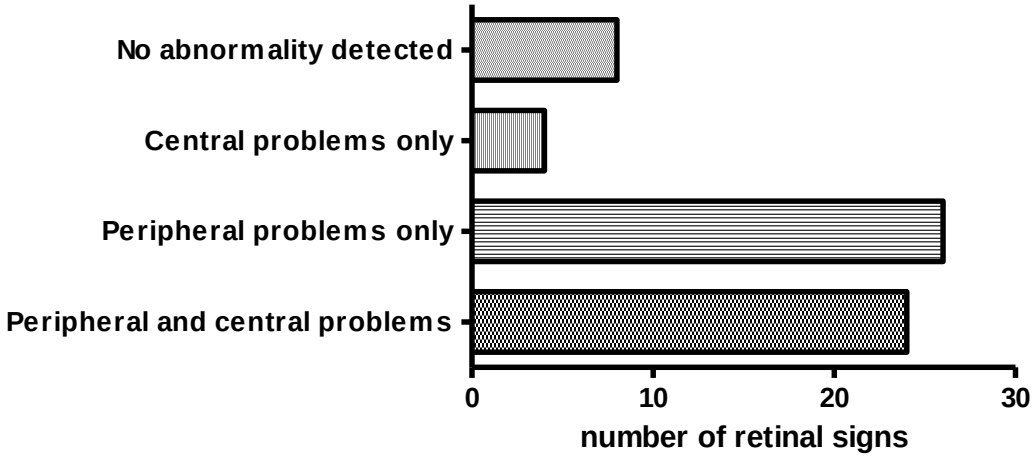


Figure 4.2-7 Retinal signs in 62 cases

4.2.7. Identification of retinal features by Optomap

Optomap images were evaluated by four other investigators who identified retinal features under masked condition. Those investigators, who were experienced optometrists or ophthalmologists, did not know the corresponding results of the dilated fundus. They had no previous experience of Optomap, but familiarized themselves with the Optomap system by viewing a sample image library provided by the database in the Optos instrument before photo evaluation. Observers were allowed to adjust the image brightness and colour contrast by adjusting the “contrast” and “gamma” buttons on the right column of the screen in the Optomap viewing program (U-Revu) provided by the Optomap manufacturer (Optos plc, United Kingdom). To achieve the image colour most

similar to our fundus observation, enhancing the “red contrast” and “gamma”, reducing the “green contrast” while leaving the “brightness” not adjusted was the common practice, but the colour adjustment was not limited to this. Optomap image observers were requested to read all the photos in each case before making a diagnosis. They were notified that there might be more than one type of retinal feature in a case, and were urged to examine every quadrant of the image carefully. Prominent choroidal/ scleral crescents around optic disc were counted as retinal feature. Observers were forced to make one answer on the findings from the choices of “no abnormality detected”, “suspected findings detected” and “cannot judge (poor image)”. Results were matched with the international classification of disease ninth version (ICD-9-CM) for each type of retinal feature, and recorded on pre-designed forms (Figure 4.2-8). The inner ring on the Figure 4.2-8 represents the equator, and the second ring represents the ora serrata. The location and size of the features were estimated. If the observer could not estimate the type of the suspected retinal feature, then they marked the suspected area as a “suspected lesion”.

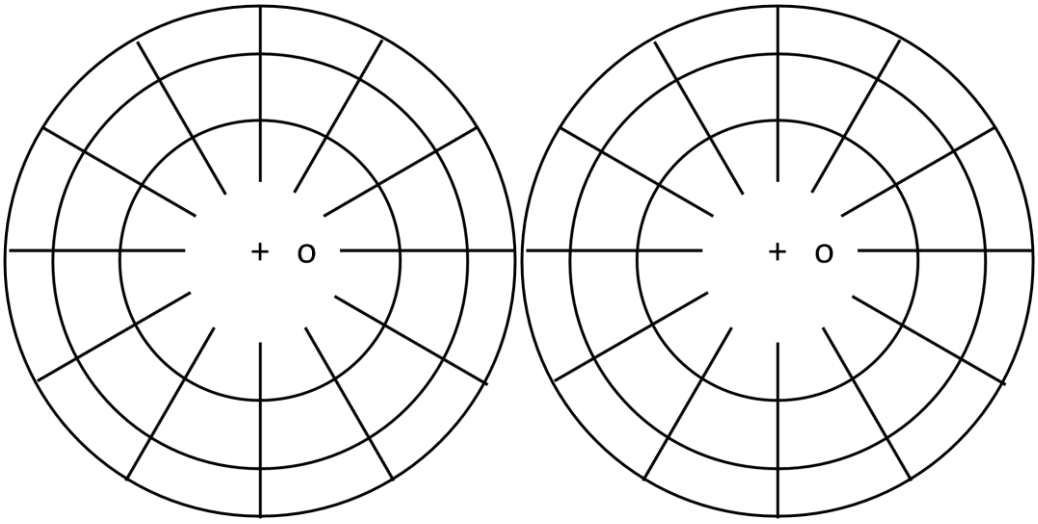


Figure 4.2-8 Record form for the estimation of location and size of the retinal features

4.2.8. Calculation of sensitivity and specificity

To calculate the sensitivity and specificity of Optomap, two approaches were employed:

1. Standard Method: Comparison of results from standard Optomap procedures and BIO procedures. In standard Optomap procedure the subject fixated on the unmovable fixation target during image capture, while in standard BIO procedures the subject was asked to look at different gazes. Thus BIO was expected to cover more fundus periphery than standard Optomap procedures.

2. Adjusted Method: Comparison of results from standard Optomap procedures and BIO procedures under the same field of view. For cases with fundal signs outside the field of the Optomap but seen on BIO, they were counted as "true negative" rather than "false negative".

Sensitivity = true positive / (true positive + false negative) ……. (1)

Specificity = true negative / (true negative + false positive) …… (2)

4.3. Results

4.3.1. Optomap image quality

The overall Optomap image quality was good. Of the 62 cases, only 2 were classified as poor and judged as unreadable by two of the investigators, leaving 60 cases for evaluation. The two cases with unreadable images were from two individuals. One case was from an elderly individual (aged 81) who suffered from macular scar. Another case was that of a young adult (aged 22) with normal ocular health, but eyelashes blocked about one-third of the image even though lid retraction was applied during image capture.

4.3.2. Sensitivity and specificity

The sensitivity and specificity of the Optomap averaged 76.4% and 71.9% respectively (Table 4.3-1). The fundal signs missed by all observers, in comparison to findings using BIO, were white-without-pressure (1 of all 24 cases), lattice degeneration (2 of all 14 cases), paramacular drusen (1 of all 5 cases), and pigmentary changes at central fundus (1 of all 2 cases). If the fundus lesions outside the field of view of Optomap were excluded in the analysis, then the sensitivity and specificity would be averaged 80.9% and 79.5% respectively (Table 4.3-2).

Table 4.3-1 Sensitivity and specificity revealed by four Optomap investigators under masked condition.

Investigator	A	B	C	D	Average
Sensitivity	75.9	77.8	85.2	66.7	76.4
Specificity	75.0	75.0	62.5	75.0	71.9

Table 4.3-2 Sensitivity and specificity with adjustment in which fundus lesions outside Optomap were excluded in the analysis.

Adjustment: Outside Optomap lesions excluded

Investigator	A	B	C	D	Average
Sensitivity	80.4	82.4	90.2	70.6	80.9
Specificity	81.8	81.8	72.7	81.8	79.5

4.3.3. Accuracy on location estimation of retinal features

Further analysis was made by dividing the fundus into posterior pole (macular and optic disc area) and four quadrants (upper right, lower right, lower left, upper left) (Figure 4.3-1). Comparisons were then made between the records from the Optomap image observers and from the binocular indirect ophthalmoscopy results (BIO results as the reference). This is to check the accuracy of the estimation of retinal features location. A low accuracy (averaged 37.7%) was found in this analysis (Table 4.3-3). It is important to note that this is not the sensitivity of the Optomap for fundus screening, but the accuracy of the Optomap in estimation of retinal features location.

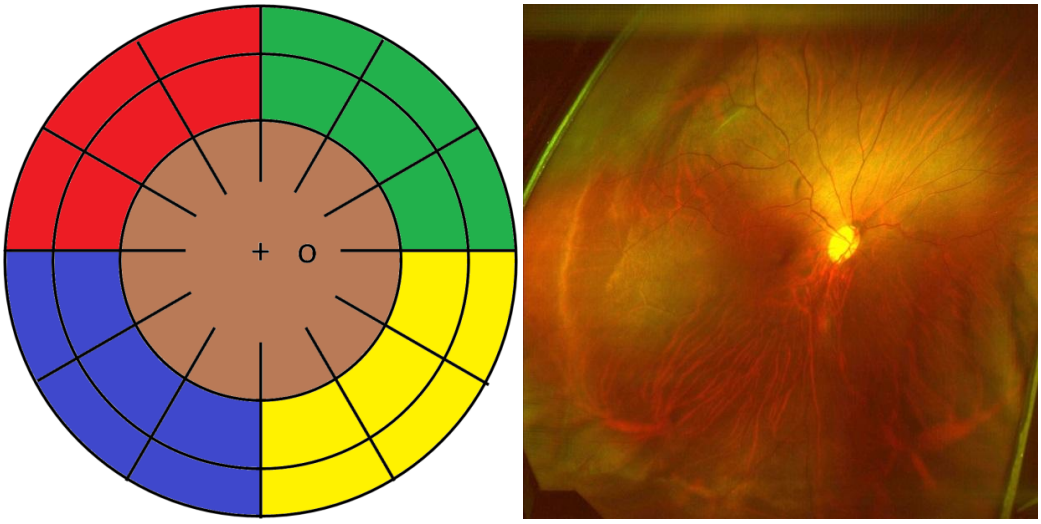


Figure 4.3-1 The division of fundus location for the empirical estimation of retinal features (left). The Optomap image which always shows a distortion in a somewhat extent (right)

Table 4.3-3 Accuracy of the estimation of retinal feature locations

Accuracy	Posterior pole	Quadrant 1(upper right)	Quadrant 2 (lower right)	Quadrant 3 (lower left)	Quadrant 4 (upper left)	Average
Investigator A	51.7	27.3	24.1	11.1	44.0	31.6
Investigator B	66.7	36.4	16.7	37.0	40.0	39.3
Investigator C	66.7	45.5	33.3	40.7	62.5	49.7
Investigator D	50.0	21.7	16.7	29.6	32.0	30.0
Average	58.8	32.7	22.7	29.6	44.6	37.7

4.4. Discussion

The sensitivity and specificity found in this study was similar to those reported by Friberg and colleagues (2003). There were no cases of diabetic retinopathy in our study, while Friberg *et al.*(2003) recruited 43 subjects with diabetic retinopathy.

In our study, the positive and negative predictive value (PV+ and PV-) were not calculated since the subject recruitment had a self-selection bias. Fifty-four out of 62 eyes had retinal features.

We categorized the types of retinal diseases among the subjects in a feature-based manner. For example, in retinal holes with laser treatment cases, we counted retinal holes and the laser burns caused by photocoagulation as two categories, rather than a single diagnosis. This increased the frequency of retinal signs as shown in Table 4.2-1. The advantage of this categorization was to facilitate the identification of "missed" retinal features with the Optomap if any, as we wanted to test whether the Optomap might "miss" something within the viewable area. Interestingly, the fundal signs that were missed by all Optomap image observers were white-without-pressure, lattice degeneration, paramacular drusen, and pigmentary changes, though only one case of each. Paramacular drusen were best detected by contrasting the red laser channel and green laser channel, while other missed fundal signs were located in the far peripheral retina apparently outside the field of the Optomap. This suggested that paramacular drusen may be difficult to detect under normal conditions, and that observation might be improved by contrasting the two colour channels.

The Optomap image provides up to a 200 degree field of view of the retina, which does not mean "from ora to ora" in one photograph. To record retinal features outside the 200 degree field, photographs need to be taken with the

patient fixating eccentrically. In our study, we expected fundus screening with the Optomap to be an easy task with minimal shots (two to five only) for each eye under the standard protocol as defined in the operation manual. Therefore, the field of view in our study was limited to the 200 degree standard view. Recently there has been another clinical modification to the technique known as a steered examination and Revelli and colleagues (2005b) reported a sensitivity and specificity with the steered examination technique of 84.28% and 98.02% respectively. In that study they instructed subjects to fixate 15 degrees eccentrically at the 12, 3, 6 and 9 o'clock positions. This may be a useful improvement to the clinical use of the instrument as the standard fixation target is currently unmovable.

Although there appears to be a significant growth in Optomap usage around the world, many eye care professionals might not be experienced in reading Optomap images. In our study the Optomap investigators had no previous experience with the instrument and were familiarized by viewing the sample image library provided by a software database before the evaluation of photographs.

In our study, the clinical modification of cotton bud eyelid retraction was performed when a subject's eyelid or eyelashes covered some part of the Optomap images. This commonly occurred among our Chinese subjects. We considered several options in lid retraction for Optomap subjects. Adhesive tape inhibits blinking for a long period. The use of a surgical lid retractor needs local anaesthetic eye drops. Using a finger to retract the lid may not be an option as with the Optomap, the subject's eye needs to be close to the instrument porthole. Thus there may be not enough room for a finger. We performed eyelid retraction using a cotton bud. The use of a new cotton bud is hygienic, comfortable for subjects and we found it easy to use. The time of corneal exposure during lid retraction is minimal.

The low accuracy of the location estimation in Optomap might be caused by the underestimation of the Optomap image observers (i.e. Observers might recognized a suspect lesion in one location but missed the others, while they counted the Optomap image in the "suspected lesion detected" category in the record form), the wrong estimation of location of the retinal features due to the distorted image of the Optomap (either the observers estimated wrongly into the neighbour quadrant, or not realized that the retinal features was across two

quadrants), the blockage of the some area of the Optomap image by eyelids or eyelashes, or the retinal features might be out of the field of view of Optomap but not under the BIO. This also explains that why the accuracy was the highest in the central region. In another study, Mackenzie *et al.* (2007) found the specificity was 85% and the sensitivity for lesions posterior to the equator was 74%, but the sensitivity for lesions anterior to the equator was 45%. The authors explained that the poorer performance of the Optomap for anterior lesions might be attributed to a reduced image quality with eccentricity and the possibility that some areas might not be imaged at the extreme periphery. They mentioned that there were particular problems at the inferior periphery due to eyelash artefact. In our study, we minimised the eyelash artefact by the lid retraction with cotton bud.

When the benefits of Optomap and the costs of preventing vision-threatening peripheral retinal diseases are considered, the instrument certainly provides an alternative for patients in whom a routine dilated examination is not indicated. The fast capture of the retinal images and the effective photo-documentation may improve the willingness of patients to have regular fundus screening in the absence of clinical indications or symptoms. Although a low accuracy of the

estimation of retinal feature locations among different quadrants was found in this study, it identified the potential subjects for further investigation like dilated fundus examination. Optomap also helps better diagnosis by providing the varying of contrasts in the two light source channels.

4.5. Conclusions

In conclusion, the sensitivity and specificity of the Optomap averaged 76.4% and 71.9% respectively in fundus screening. The sensitivity and specificity found in this study was similar to a previous report. Optomap has certain advantages, as a screening tool, it permits fundus examination without the use of a mydriatic agent, which is more comfortable for the patients. This helps the practitioner to decide whether further investigation on fundus examination if there is absence of strong indication of dilated fundus examination. It also facilitates the keeping of permanent digital record of the findings. However, there are still some shortfalls, including that retinal lesions at the outside edges of the retina might not be identified, the colours of the Optomap are the artificial combination of two laser channels, shown in a distorted image. The Optomap can be complementary to the standard dilated fundus examination but not a substitute, especially in a high risk group for the occurrence of retinal lesions, such as the high myopic population.

5. Chapter Five. Prevalence and risk factors of myopic related retinal changes among 12 to 18 year old Hong Kong Chinese high myopes

5.1. Introduction

As discussed in the literature review (Chapter 1), Hong Kong has large group of people having myopia, and the trend of myopia progression was observed during school ages. Some of them will finally become -6 D or more, which is high myopia. Among the Chinese, an apparently susceptible population in developing myopia, the demarcation between physiologic and pathologic myopia might be less clear when someone is continuously having myopia progression. There was a high proportion of moderate myopes (i.e. -3.00 D to less than -6.00 D) among the Chinese myopic population (Goh and Lam, 1994). While a considerable prevalence of retinal degenerations was found associated with high myopia (Lai *et al.*, 2008), it is still unknown whether the high prevalence of myopic schoolchildren will eventually progress to high myopia and result in more people having myopic degeneration.

High myopia is not only an optical problem, but also higher risk of having ocular complications including higher incidence of cataracts (Lim *et al.*, 1999, Younan *et al.*, 2002), glaucoma (Ponte *et al.*, 1994, Wong *et al.*, 2003) and retinal abnormalities (Hyams and Neumann, 1969, Karlin and Curtin, 1976, Celorio and Pruett, 1991, Pierro *et al.*, 1992, Yura, 1998). While these problems are affected by aging, some of them might occur at a younger age, e.g. retinal detachment, which caused serious vision threat and even blindness (Rosner *et al.*, 1987, Logan *et al.*, 2004).

There is still little we know about how the retina changes in early life as affected by high myopia. Earlier studies provide data on retinal changes in the general adult population with myopia of over -6 D, but rarely focused on the change in age before adulthood. We know that some of the schoolchildren progress to -6 D or more of myopia before reaching the adult stage, and the population of high myopic children is increasing (Lin *et al.*, 2004). There is a need to know more about whether there are potential hazards in this group of population.

5.2. Previous reports on prevalence of myopic related retinal changes

In adult populations, there are many reports on the prevalence of retinal degeneration in highly myopic eyes (Hyams and Neumann, 1969, Curtin and Karlin, 1971, Kirker and McDonald, 1971, Celorio and Pruett, 1991, Pierro *et al.*, 1992, Ho *et al.*, 1994, Gozum *et al.*, 1997, Lam *et al.*, 2005, Lai *et al.*, 2008). The results vary depending on the ethnicity of the subject group, the method of examination, classification of retinal lesions, and the study criteria. Those retinal degenerations included central retinal degeneration including lacquer crack, posterior staphyloma, Fuch's spot and chorioretinal atrophy. At the fundus periphery, the occurrence of pigmentary degeneration, white-without-pressure, lattice degeneration, retinal hole, retinal break and retinal detachment were associated with high myopia. Central retinal lesions may cause a reduction in visual acuity, while myopic degeneration is reported to be a major cause of legal blindness in many developed countries (Perkins, 1979, Tokoro, 1998). Though peripheral retinal degenerations might not affect central vision, they are the risk factors of retinal detachment, and this might lead to serious vision threat and even blindness (Lewis, 2003).

Gonin (1921, 1930, cited by Hyams and Neumann (1969)), commented on the role of retinal breaks in the etiology of retinal detachment, and Duke-Elder and Dobree (1967, cited by Hyams and Neumann (1969)), reported that about two-thirds of retinal detachments occur in myopic eyes. Hyams and Neumann (1969) investigated the peripheral retina in 332 myopic eyes. They found that the prevalence of retinal breaks in myopic eyes more than -6 D was 13%. The frequency of retinal breaks was correlated with greater age, but not significantly correlated with degree of myopia.

Curtin and Karlin (1971) presented the prevalence of chorioretinal degeneration in myopic eyes according to the effect of age and axial length, and showed that degeneration increases with age and axial length (cited by Curtin (1985)).The prevalence of chorioretinal atrophy was 23% in eyes with axial length longer than 24.5 mm. Lacquer cracks was found 4.3% in eyes with axial length longer than 26.5 mm, and white without pressure was found in 54% of the eyes with axial length 33 mm.

Kirker and McDonald (1971) reported that 22% of the high myopic eyes (- 6 D myopia or more) showed peripheral retinal degenerations, including pigmentary

degeneration, lattice degeneration, white-without-pressure, retinal holes, and focal pigmentation. The incidence of lattice degeneration was reported to be only three percent. However, the categorization of "snail track degeneration" in the study was not categorized in lattice degeneration, but in white-without-pressure. This was different from other comments that snail track degeneration was considered as a variant of lattice degeneration (Shukla and Ahuja, 1981, Tarasewicz and Chan, 2006).

Celorio and Pruett (1991) studied 436 eyes of 218 subjects with myopia -6 D or more for the prevalence of lattice degeneration. They stated the prevalence was 33%. Young adults in the age group of 21 to 40 year were most prevalent, and the lattice degenerations were located more often in temporal quadrants.

Pierro *et al.* (1992) examined 513 eyes from 513 patients with axial length ranged from 24.0 mm to 36.3 mm, and found the most common lesions were posterior vitreous detachment (47.7%), pavingstone degeneration (27.1%) and white with or without pressure (22.8%). There were 16.9% pigmentary degeneration, 13.2% lattice degeneration, and 12.1% retinal holes or tears. The least frequent retinal lesion was retinal detachment (5.6%). Pierro *et al.* (1992)

revealed the positive correlation between axial length and presence of white-without-pressure, lattice degeneration and pavingstone degeneration. However, no significance was shown between axial length and retinal detachment, retinal holes, and peripheral pigment.

Among the Chinese population, Ho *et al.* (1994) examined 170 high myopic (>-6 D) college students in Taiwan and discovered that in myopic eyes of –8 D to –13 D, the prevalence of white with pressure and snail tract degenerations were found to be above 60% and above 30%, respectively. The prevalence of lattice degeneration was 25.9% for all subjects involved, and it was highly correlated with axial length. The study provided details on the prevalence of peripheral retinal degenerations of the high myopes.

Lam *et al.* (2005) examined 213 eyes in 213 high myopes in Hong Kong ranging from – 6 D to – 27 D. They pointed out that the most common peripheral retinal degeneration in high myopes was pigmentary degeneration, having a prevalence of 51.2%. The prevalence of white-without-pressure, lattice degeneration, retinal hole or tear, and pavingstone degeneration was 31.0%, 12.2%, 7.5%, and 5.2% respectively. The prevalence of retinal detachment was only 0.5%. The

prevalence of lattice degeneration reported was lowest among previous studies, except the report from Kirker and McDonald (1971). It was half of the percentage reported from Ho *et al.* (1994), which also selected Chinese as the subjects' ethnic group.

Lai *et al.* (2008) examined 337 high myopic subjects in Hong Kong with myopia more than -6 D, with a mean age of 36 years. Posterior pole lesions were found in 11.3% eyes, and 56.1% eyes had peripheral retinal lesions. Posterior staphyloma was found in 7.7% of the eyes. The prevalence of chorioretinal atrophy, lacquer crack, Fuch's spot were 2.7%, 1.8%, and 0.3%, respectively. For peripheral lesions, the prevalence of pigmentary degeneration, white-without-pressure, lattice degeneration and retinal hole or break were 37.7%, 21.1%, 13.6%, 6.2%.

Liu *et al.* (2010) studied the prevalence of myopic retinopathy (defined as having posterior staphyloma, lacquer cracks, Fuchs' spot of the macula, and myopic chorioretinal atrophy at the posterior pole) in the Beijing Eye Study in Greater Beijing. They examined 214 subjects with -6 D or more myopia, aged 40 and over, and reported prevalence of myopic retinopathy of 40.4% in eyes with -6 D

to <-8 D, 72.9% in eyes with -8 D to <-10 D, and 89.6% in eyes with -10 D or more.

High myopia in children might have association with retinal problems. Logan *et al.* (2004) invited 85 eligible subjects, and investigated the association of high myopia (-5 D or more) and ocular and systemic disease by examining 28 children in age ranged from 3 to 10 years with both optometric and ophthalmological examination. They noted that there were 7 children (25%) were having ocular problems, two children showed retinal dystrophy, and 5 children were amblyopic. However, since the sample size was limited, the prevalence reported might be somewhat different from the prevalence in the general population. Bansal and Hubbard (2010) retrospectively reviewed the charts of all children aged 10 years or younger with high myopia (-6 D or more) who underwent eye examination by a single retina specialist between January 2001 and December 2008. There were 54 eyes from 30 subjects with mean age of 6 ± 3 years. They found peripheral retinal findings in 33% of eyes, with lattice degeneration (20%), white without pressure (11%), retinal holes with subretinal fluid (4%) and vitreoretinal tuft (2%).

Table 5.2-1 summarizes the prevalence of myopic related retinal changes in adults from previous reports. Among the studies, the most frequent retinal changes are peripapillary atrophy (96.6% - 97.9%), white with or without pressure (22.8% - 60%), pigmentary degeneration (16.9% - 51.2%) and posterior vitreous detachment (47.7%). The vision threatening lesion, retinal break or tear, was found in 7.5% - 13% of myopic eyes with myopia of more than -6 D.

Since previous studies report that a considerable proportion of the high myopic adult population have retinal changes, it is important to know whether these retinal changes begin in young children, especially those sight threatening potential and its predisposing factors.

Table 5.2-1 Summary of prevalence of retinal changes in high myopic eyes

Retinal lesion	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)
Optic nerve crescent		95-100*							
White Without Pressure			22.8	5	>50	31.0	21.1		11
Lattice degeneration		11	13.2	3	25.9	12.2	13.6		20
Microcystoid degeneration									
Peripheral pigmentary degeneration			16.9	14		51.2	37.7		
Peripapillary atrophy								96.6-97.9	
Retinal hole or tear	13		12.1	2		7.5	6.2		4
Chorioretinal degeneration		10-90*		22					
Retinal detachment			5.6		2.4	0.5			
Pavingstone degeneration			27.1			5.2			
Posterior staphyloma		19					7.7		
Lacquer crack		4.3					1.8		
Fuch's spot		5.2					0.3		
Retinal tuft									2
Central chorioretinal degeneration				13			2.7		
Posterior vitreous detachment			47.7						
Any posterior pole lesion							11.3	40.4-89.6*	
Any peripheral lesion							56.1		

#All numbers in percentage; * Percentage increased as axial length / myopia increased. (a) Hyams and Neumann (1969); (b) Curtin and Karlin (1970, 1976); (c) Kirker and McDonald (1971); (d) Pierro *et al.* (1992); (e) Ho *et al.* (1994); (f) Lam *et al.* (2005); (g) Lai *et al.* (2008); (h) Liu *et al.* (2010); (i) Bansal and Hubbard (2010)

5.3. Risk factors of myopic related retinal changes

Various potential risk factors were studied in previous reports, including age, gender, age of onset of myopia and optical components like axial length. These factors are reviewed and discussed in below.

5.3.1. Age

There were little information available as to possible risk factors associated with retinal pathology, including age and gender. Celorio and Pruett (1991) revealed that lattice degeneration occurred most frequently in young adults aged 21 to 40 years. Gozum *et al.* (1997) pointed out that the presence of chorioretinal atrophy, Fuch's spot, posterior staphyloma and posterior vitreous detachment were positively correlated with age. However, the presence of white-without-pressure was inversely correlated with age.

5.3.2. Gender

Female high myopes (-6 D or more) are more likely to have Fuch's spots, while male high myopes are more common to have white-without-pressure (Gozum *et al.*, 1997).

5.3.3. Age onset of myopia

It is a general concept that as age increases, the incidence of retinal degeneration increases. However, high myopia is also found to be related to retinal degeneration at young age. Tokoro (1998) reported on the prevalence of chorioretinal atrophy among Japanese with high myopia (>-8 D), and found that diffuse choroidal atrophy starts from as young as 5 to 9 year-old, while patchy atrophy begins from 10 to 14 year-old. However, the study included all high myopic subjects (>-8 D) in one group, so there is no correlation to be derived between degree of myopia and age of onset of chorioretinal atrophy.

5.3.4. Optical components

Axial length has a long history as a potential risk factor of myopic related retinal changes, since an increase in axial length implies a bigger eye and thus a change might happen with increased surface area of retina. Curtin and Karlin (1971) reported that an axial length of 26.5 mm or more is associated with posterior retinal degeneration, including Fuch's spots and lacquer cracks (cited by Curtin (1985)). Karlin and Curtin (1976) also reported an increase of the prevalence of

chorioretinal degeneration, including white without pressure, pigmentary degeneration, pavingstone degeneration and lattice degeneration, with increased axial length. Lattice degeneration has been detected in 11% of eyes with 26.5 mm or more in axial length (Karlin and Curtin, 1976). However, corneal curvature and the total degree of myopia of the subjects were not categorized in the prevalence pattern. Pierro *et al.* (1992) examined 513 eyes from 513 patients with axial length ranging from 24.0 mm to 36.3 mm, and revealed a positive correlation between axial length and presence of white-without-pressure, lattice degeneration and pavingstone degeneration. However, no correlation was shown between axial length and retinal detachment, retinal holes, and peripheral pigment.

Yura (1998) also showed that lattice degeneration was more frequent with longer axial length. This study also noted, for the same axial length, lattice degeneration was more frequent in eyes without posterior staphyloma than eyes with posterior staphyloma. It was suggested that the reason might be due to different types of eye globe elongation; i.e. the entire elongation happened in eyes without staphyloma, while an additional elongation only happened at the posterior pole in eyes with staphyloma.

However, some studies showed inconsistency about the positive correlation of peripheral retinal degeneration and axial length. Celorio and Pruett (1991) discovered that the lowest prevalence of lattice degeneration was found among eyes of axial length 32 mm or greater, though the highest prevalence was among eyes of axial length 26.0 mm to 26.9 mm. Gozum *et al.* (1997) investigated 212 eyes of 109 patients with -6 D or more myopia in Istanbul, and, surprisingly, they pointed out that with longer axial length, the presence of white-without-pressure was significantly lower ($p = 0.039$), whilst the presence of pavingstone degeneration was higher ($p = 0.016$). Also, they reported that no significant relationship was found between axial length and lattice degeneration, while the incidence of lattice degeneration was stated to be higher in high myopes compared with emmetropes. They proposed that hereditary factors might involve in the existence of lattice degeneration, which caused the results to fail to show any relationship between axial length and lattice degeneration.

There is little information concerning other optical components and myopic related retinal changes in the literature. Liu *et al.* (2010) reported subjects with "myopic retinopathy" (i.e. posterior staphyloma, lacquer cracks, Fuchs' spot of

the macula, and myopic chorioretinal atrophy at the posterior pole) have deeper anterior chambers.

5.3.5. Gaps in the knowledge

There are many reports on the prevalence of myopic related retinal changes. However, the prevalence varies widely among different studies, even within the same ethnicity (i.e. Hong Kong-Chinese compared with Taiwan-Chinese). Also, to the best of our knowledge, there is no available information on the prevalence of myopia related retinal changes associated with high myopia among the younger age group among a Chinese population.

Among the Chinese, a population susceptible to the development of myopia, the demarcation between physiologic and pathologic myopia might be less clear due to the continuous progression of myopia. There are a high proportion of moderate myopes (i.e. -3.00 D to less than -6.00 D) among the Chinese myopic population (Goh and Lam, 1994). While a considerable prevalence of retinal degenerations was found associated with high myopia (Lai *et al.*, 2008), it is still

not known whether the high prevalence of myopic schoolchildren will eventually progress to high myopia and result in more people having myopic degeneration.

5.4. Objectives

The following study may help establish the prevalence of myopic related retinal changes in a younger high myopic age group and this will also provide useful information to educate the public on this ocular health issue and to caution vulnerable myopic subjects.

5.5. Method

The following sections described the details of this study, including subject recruitment, personal data collection, refractive status measurement, biometry, documentation of retinal characteristic and IOP measurement.

5.5.1. Subject recruitment

Subjects were recruited during January 2005 to June 2009 from (1) two newspaper advertisements in the Hong Kong Economic Times and Mingpao, (2) invitation letters sent to secondary schools, (3) leaflets delivered in The Hong Kong Polytechnic University Optometry Clinic, and (4) posters in the Hong Kong Polytechnic University campus. Young school children subjects aged from 12 to 18 year-old were recruited. Data from only one eye was used in this study. The eye with higher spherical equivalent error was used for analysis for each subject. The inclusion criteria used for refractive error was that the spherical component measured by cycloplegic-autorefraction should be equal or more than -5.25 DS, and the spherical equivalent error equal or more than -6.00 D. Subjects under orthokeratology treatment or those who received refractive surgery were excluded. Subjects with media opacities causing unclear fundus observation were also excluded from the study. Informed consent was obtained from subjects or their guardian prior to the measurement.

5.5.2. Personal data collection and history of myopia progression

Personal data including age, gender, ethnicity, age of onset of myopia, history of ocular and systemic diseases, history of ocular surgery, trauma and injury, symptoms of retinal detachment, and family ocular and general history was gathered in the first visit with a standardised questionnaire (Appendix: Subject History Checklist). The onset of myopia was found asking the subject's parent when the subject was first diagnosed to have myopia, no matter whether the subject needed to have optical correction or not.

5.5.3. Refractive status measurement

The amount of refractive error was determined with the Shin-Nippon SRW-5000 auto-refractor after cycloplegia (using 2 drops of Tropicamide 1.0%, after Oxybuprocaine Hydrochloride 0.4% local anesthesia), followed by cycloplegic auto-refraction. Best corrected visual acuity was assessed by logMAR chart.

5.5.4. Biometry, documentation of retinal characteristics and tonometry

Axial length was measured using the IOL Master (Zeiss Humphrey). Five effective measurements were performed and the mean reading was used for data analysis. Keratometry measurements were carried out with a Medmont corneal topographer. A dilated fundus examination was performed using BIO and Volk lens, under the mydriatic effect of Tropicamide 1.0%, and recorded in pre-designed form. Dilated pupil size was at least 6 mm, measured by Haab scale. Photodocumentation of fundal changes were made with the Optomap and digital fundus camera whenever possible. Intraocular pressure was measured by non-contact tonometer prior to pupil dilation.

5.6. Results

5.6.1. Subjects demographics

One hundred and twenty eyes from one hundred and twenty subjects were analyzed in this study. One hundred and seventeen subjects (97.5%) have lived in Hong Kong since birth. All subjects have lived in Hong Kong for the last 5 years or more. No subject reported to have systemic diseases, including diabetes and hypertension. Forty-eight subjects (40%) had a family history of high myopia. Thirty-three subjects (27.5%) reported to have ocular symptom of stable floaters. Two subjects (1.7%) had experienced flashes symptom before this study. Thirteen subjects (10.8%) had family histories of retinal disease.

Among the recruited 120 subjects, a hundred and two subjects (85%) met inclusion criteria bilaterally, while 18 subjects only met inclusion criteria in one eye. There were 20 anisometropic cases (difference in spherical component 1.50 D or more) among our subjects.

As the more myopic eye was used for analysis in each subject, fifty-four right eyes (45%) and sixty-six left eyes (55%) were used in the analysis. There was no significant difference in mean myopia, astigmatism, SER and axial length between right and left eyes (unpaired t-test, $p = 0.194$, $p = 0.147$, $p = 0.116$ and $p = 0.458$ respectively).

The mean age of the subjects was 14.83 ± 1.58 years, ranged from 12 years-old to 18 years-old. There were 61 boys (50.8%) and 59 (49.2%) girls in this study. Figure 5.6-1 shows the age distribution among recruited subjects.

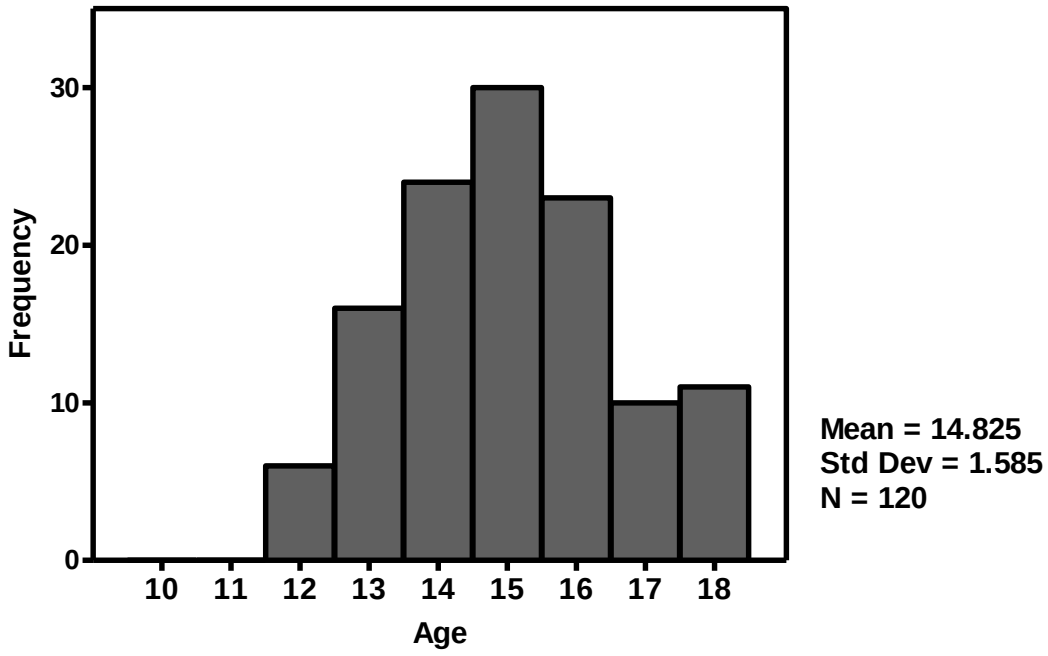


Figure 5.6-1 Age distribution of recruited subjects

5.6.2. Refractive status

In our study, 70% (n = 84) of subjects has reached 0.00 LogMAR or better corrected visual acuity. Only one eye had visual acuity worse than 0.20 LogMAR. The refractive status of the eyes that met the inclusion criteria is shown in Table 5.6-1 and its frequency distribution is plotted in Figure 5.6-2.

Table 5.6-1 Refractive status of eyes that met inclusion and exclusion criteria

	Mean	SD	Range
Sphere	-7.61	1.68	-5.25 to -16.25
Cylinder	-1.60	0.93	0.00 to -4.50
SER	-8.41	1.82	-6.00 to -17.13
Corneal curvature	43.69	1.42	40.19 to 47.90

* All units were in dioptre (D), n = 120

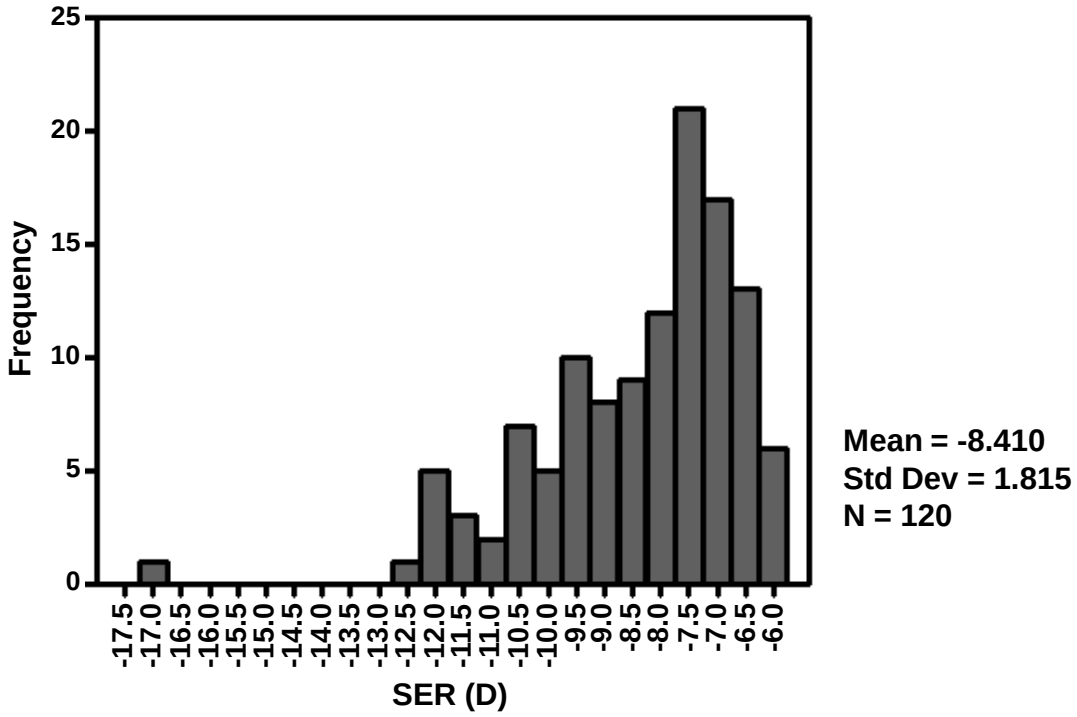


Figure 5.6-2 Frequency distribution of SER among subjects

The axis of astigmatism among the subjects was predominantly with-the-rule astigmatism (axis between 150 and 30 degrees), comprising 90.8% (n = 109) of the eyes. Only 3.3% (n = 4) of the eyes had against-the-rule astigmatism (axis between 60 and 120 degrees). Seven eyes (5.8%) had oblique astigmatism. Mean corneal astigmatism was -1.81 ± 0.71 DC. Mean corneal astigmatism was 0.21 D greater than the mean refractive astigmatism (paired t-test, $p < 0.001$).

5.6.3. Axial length

The mean axial length was 26.91 ± 0.88 mm. Figure 5.6-3 shows the distribution of axial length among the eyes analyzed. Boys had significantly longer axial length than girls (unpaired t-test, p = 0.005).

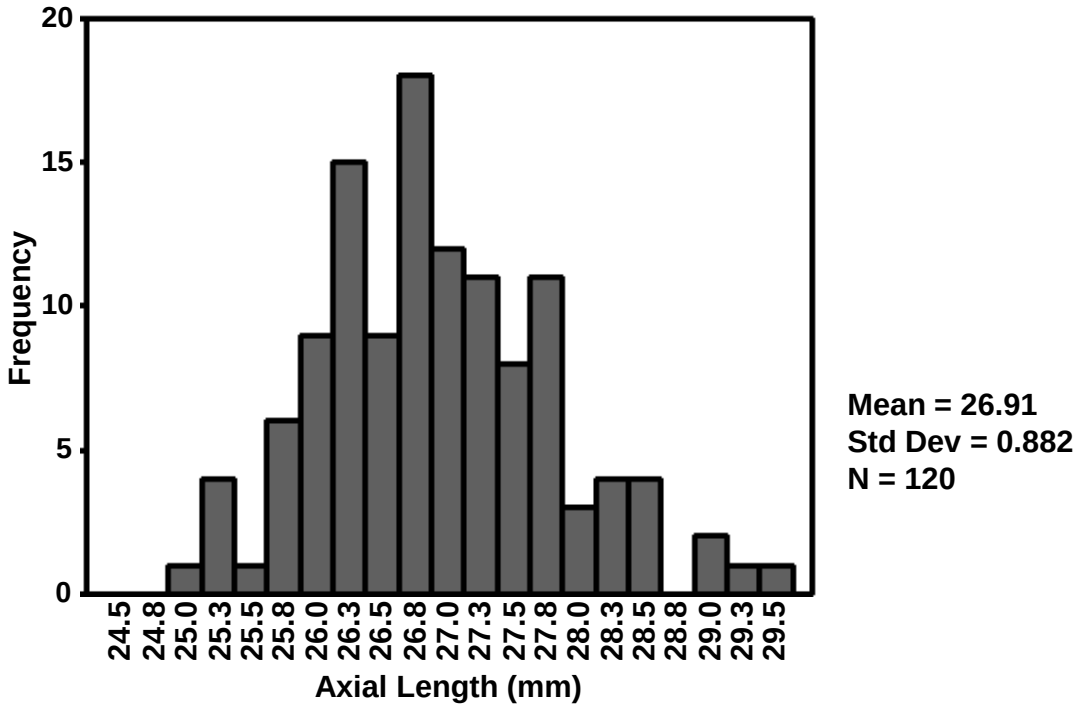


Figure 5.6-3 Frequency distribution of axial length among subjects

5.6.4. Age of onset of myopia

The mean age of onset of myopia of these high myopic subjects was 6.54 ± 1.52 years. There was no difference in mean age of onset of myopia between boys and girls (unpaired t-test, p = 0.11). The younger age of onset of myopia was associated with more minus SER (Pearson's coefficient 0.563, p < 0.001, R^2 = 0.317) (Figure 5.6-4). More years of myopia leads to more myopia (Pearson's coefficient -0.278, p < 0.001), despite the poor goodness of fit (R^2 = 0.0077) (Figure 5.6-5).

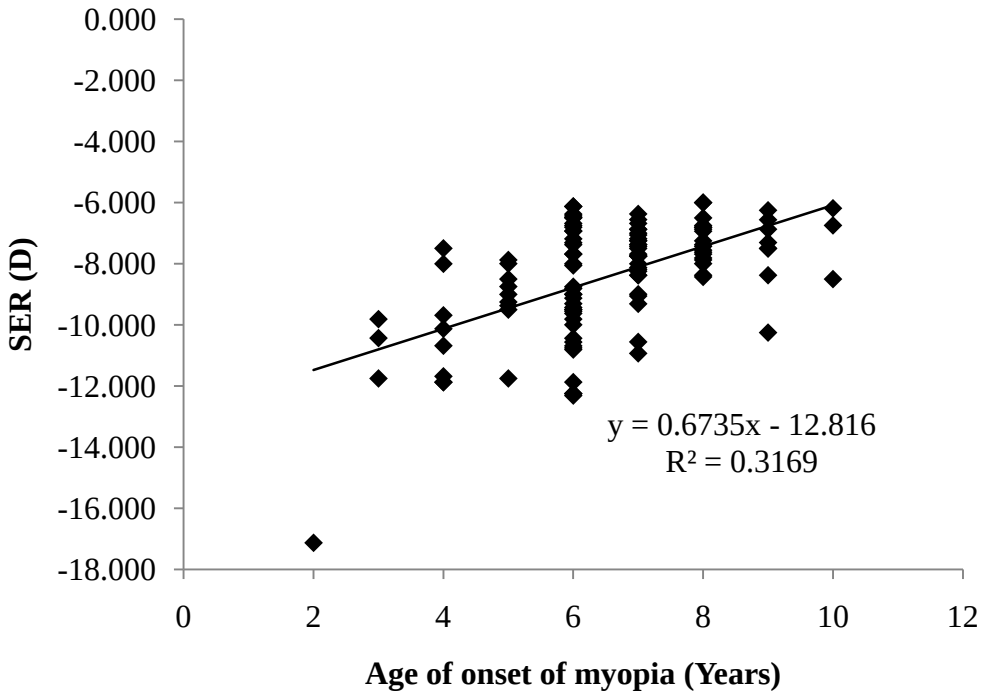


Figure 5.6-4 Scatterplot of onset of myopia versus SER

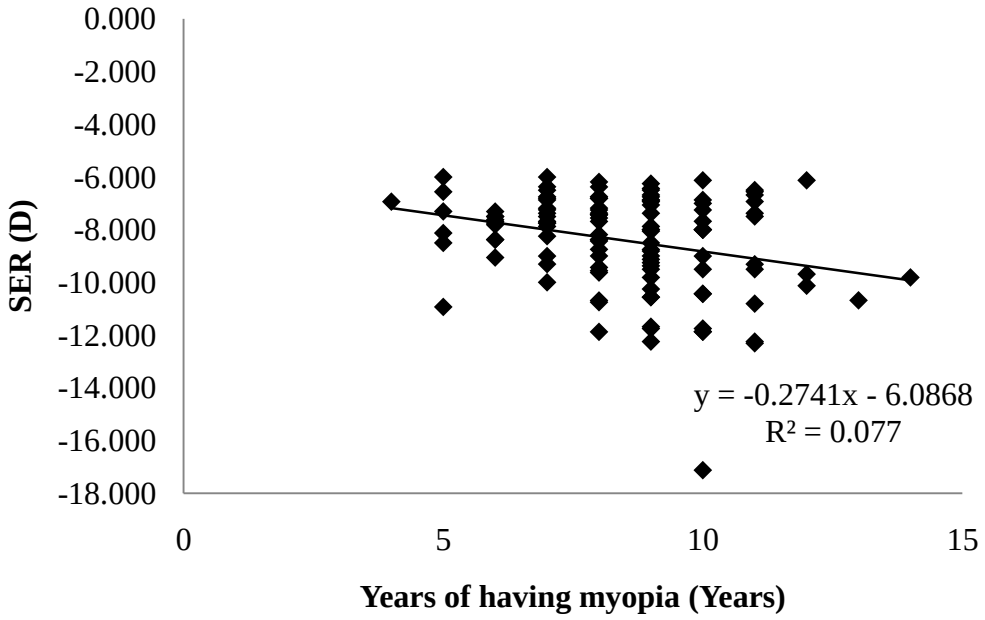


Figure 5.6-5 Scatterplot of years of having myopia versus SER

5.6.5. Myopia progression

The mean number of years of having myopia was 8.09 ± 1.82 years and ranged from 4 years to 13 years. The SER was divided by the number of years having myopia and the averaged rate of myopia progression was -0.93 ± 0.26 D per year. There was a gender difference (unpaired t-test, $p < 0.001$) in our subject group. The mean rate of myopia progression in girls (-1.03 ± 0.28 D) was greater than in boys (-0.84 ± 0.21 D). This was due to the fact that the mean age of girls (14.61 ± 1.53 years) in our subjects were younger than boys (15.41 ± 1.58 years) (unpaired t-test, $p = 0.006$).

5.6.6. Gender differences with age, SER, axial length and IOP

Comparisons have been made between genders for age, SER, spherical error, cylindrical error, axial length and IOP. The mean age and axial length was significantly greater in boys (15.41 ± 1.58 yrs and 27.13 ± 0.93 mm respectively) than in girls (14.61 ± 1.53 yrs and 26.68 ± 0.78 mm) (unpaired t-test, $p = 0.006$ and $p = 0.005$ respectively). Table 5.6-2 shows the results of comparisons.

Table 5.6-2 Comparisons between genders for age, onset of myopia, refractive error, axial length and IOP

Mean	Boys	Girls	p value
Age	15.41 ± 1.58	14.61 ± 1.53	0.006*
Onset of myopia	6.43 ± 1.61	6.66 ± 1.42	0.399
Spherical error	-7.37 ± 1.76	-7.76 ± 1.41	0.117
Cylindrical error	-1.62 ± 0.94	-1.58 ± 0.92	0.829
Corneal astigmatism	-1.82 ± 0.67	-1.81 ± 0.75	0.920
SER	-8.18 ± 1.89	-8.65 ± 1.72	0.164
IOP	15.97 ± 2.37	16.70 ± 2.70	0.116
AXIAL	27.13 ± 0.93	26.68 ± 0.78	0.005*

* $p < 0.05$, unpaired t-test, n = 120

5.6.7. Correlations of SER and axial length

There were significant correlations between SER and axial length in high myopic schoolchildren eyes (Pearson's correlation, $p< 0.001$, $r = -0.439$) in both eyes. The regression line was SER = 15.89 – 0.90 x axial length. Figure 5.6-6 shows the scatter plot of the regressions.

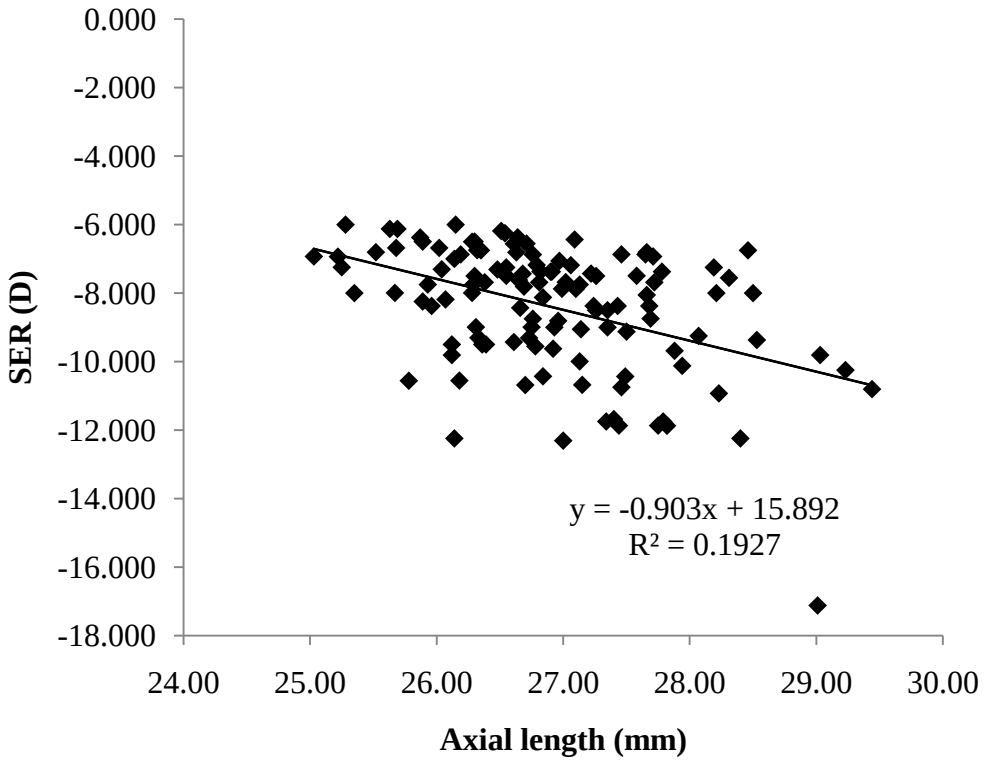


Figure 5.6-6 Regression of SER and axial length

5.6.8. Frequencies of retinal lesions

The frequencies of retinal lesions among the eyes are shown in Table 5.6-3 **.** Previous studies (Hyams and Neumann, 1969, Kirker and McDonald, 1971, Curtin, 1985, Pierro *et al.*, 1992, Ho *et al.*, 1994, Yura, 1998, Lewis, 2003, Lam *et al.*, 2005, Lai *et al.*, 2008, Bansal and Hubbard, 2010, Liu *et al.*, 2010) considered various lesions as myopic related retinal changes and they are adopted in this study. About half of the eyes had optic nerve crescents (52.5%) and white-without-pressure (WWOP) (51.7%), the extension of the WWOP is illustrated in the Table 5.6-4. Besides, three eyes (2.5%) had peripapillary atrophy. Two eyes (1.7%) had retinal tufts and one eye (0.8%) had an atrophic retinal hole. Four eyes (3.3%) had lattice degeneration. Three eyes (2.5%) had snail-track degeneration. Five (4.2%) right eyes had pigmentary degeneration, and six eyes (5%) had microcystoid degeneration. One eye (0.8%) had a chorioretinal scar.

The frequencies of WWOP in multiple quadrants are shown in Table 5.6-4. About half of our subjects had no WWOP, and 30% of them had WWOP in one

quadrant. Extensive WWOP surrounding the peripheral retina was observed in 8% of subjects.

To observe whether there was any difference between the selected eyes and non-selected eyes, we also looked at the data of the fellow eye. The fellow eye of the subjects still had retinal lesions, for instance, one eye had retinal detachment and one eyes had atrophic retinal holes, even though they were not counted in our study.

Table 5.6-3 Frequencies of myopia related retinal changes observed in the eyes analyzed

Retinal lesion	no. of eyes	percentage
Optic nerve crescent	63	52.5%
WWOP	62	51.7%
Lattice degeneration	4	3.3%
Snail-track degeneration	3	2.5%
Microcystoid degeneration	6	5%
Peripheral pigmentary degeneration	5	4.2%
Peripapillary atrophy	3	2.5%
Retinal hole or tear	1	0.8%
Chorioretinal degeneration	1	0.8%
Retinal detachment	0	0%
Pavingstone degeneration	0	0%
Posterior staphyloma	0	0%
Lacquer crack	0	0%
Fuch’s spot	0	0%
Retinal tuft	0	0%
Central chorioretinal degeneration	0	0%
Posterior vitreous detachment	0	0%
Any posterior pole lesion	66	55%
Any peripheral retinal lesion	74	61.7%

(n = 120)

Table 5.6-4 Frequency of WWOP in high myopic school-children

Quadrants	Frequency	Percentage
0	58	48.3
1	36	30
2	10	8.3
3	6	5.0
4	10	8.3

(n = 120)

5.6.9. Multiple retinal lesions in the same eye

Some eyes had more than one retinal lesion. Table 5.6-5 and Table 5.6-6 show the distribution of frequencies of having one or more lesions and peripheral lesions in the same eye respectively. Among those eyes with retinal lesions, about half of them had only one lesion, 40% of them had two retinal lesions within the same eye, and one eye (7%) had five retinal lesions.

Table 5.6-5 Frequency of multiple retinal lesions

No. of lesions	Frequency	Percentage
0	26	21.7
1	48	40.0
2	38	31.7
3	7	5.8
5	1	0.8
Total	120	100

For peripheral retinal lesions, 46 eyes (38.3%) had no peripheral lesions. In the eyes with peripheral retinal lesions, the majority of them had only one lesion (Table 5.6-6). Only 7 eyes had two lesions and 1 eye had four lesions.

Table 5.6-6 Frequency of multiple peripheral retinal lesions

No. of lesions	Frequency	Percentage
0	46	38.3
1	66	55.0
2	7	5.8
4	1	0.8
Total	120	100

(n = 120)

5.6.10. Comparisons between eyes with and without retinal lesions

The followings were the comparisons between eyes with and without retinal lesions in the groups of subject age, gender, refractive status, IOP, myopia onset and myopia progression rate.

Although eyes from boys had greater mean age and longer axial length, there was no significant relationship between gender and the occurrence of retinal lesions (Chi's square for all retinal lesions = 0.965, df = 1, p = 0.326, n = 120) (Chi's square for peripheral retinal lesions = 2.710, df = 1, p= 0.100, n = 120), and also in age-matched comparisons (Fisher's tests, p > 0.05 in all age-matched analyses) (Table 5.6-7).

Table 5.6-7 Frequency of retinal lesions in boys and girls

Retinal lesions	Boys	Girls
Total retinal lesions	50	44
Peripheral retinal lesions	42	32

(n = 120)

We grouped those eyes with any kind of retinal lesions mentioned in the Table 5.6-3 as the retinal lesion group. The following table shows the statistics of subject age, refractive error, axial length and IOP in two groups, with and

without retinal lesions (Table 5.6-8). There was a significant difference in SER (unpaired t-test, $p = 0.048$, $t = 1.997$, $df = 118$, $n = 120$), and astigmatism (unpaired t-test, $p = 0.016$, $t = -2.454$, $df = 118$, $n = 120$). The mean axial lengths between two groups were marginally insignificant (unpaired t-test, $p = 0.078$, $t = -1.775$, $df = 118$, $n = 120$). Eyes with lesions was significantly greater in astigmatism and SER, while astigmatism was significantly correlated with SER (Pearson's correlation, $r = 0.413$, $p < 0.001$, $n = 120$). There was no significant difference observed in age, years of having myopia, age of onset of myopia, myopia progression rate and intra-ocular pressure between eyes with and without lesions (unpaired t-test, $p > 0.05$).

Table 5.6-8 Mean values of parameters in eyes with and without retinal lesions

Parameters	Eyes without lesions (n = 26)	Eyes with lesions (n = 94)	p*
Age (year)	15.00 ± 1.63	15.01 ± 1.60	0.952
Spherical error (D)	-7.18 ± 1.33	-7.73 ± 1.74	0.142
Cylindrical error (D)	-1.22 ± 0.87	-1.71 ± 0.92	0.016
Corneal astigmatism (D)	-1.59 ± 0.72	-1.87 ± 0.69	0.065
SER (D)	-7.79 ± 1.38	-8.58 ± 1.89	0.048
Axial length (mm)	26.64 ± 0.78	26.99 ± 0.90	0.078
IOP (mmHg)	16.70 ± 2.76	16.22 ± 2.50	0.407
Myopia progression rate (D/year)	-0.89 ± 0.24	-0.95 ± 0.26	0.307
Onset of myopia (year)	6.50 ± 1.36	6.55 ± 1.56	0.875

*Unpaired t-test, n = 120

Those eyes with any kind of peripheral retinal lesions mentioned in the Table 5.6-3 were counted in the eyes of the peripheral retinal lesion group. Table 5.6-9 shows the statistics of subject age, refractive error, axial length and IOP in two groups, with and without peripheral retinal lesions. Eyes with peripheral retinal lesions had significantly longer axial length and higher IOP. The difference in mean SER between the two groups was marginally insignificant (p = 0.078).

Table 5.6-9 Mean values of parameters in eyes with and without peripheral retinal lesions

Parameters	Eyes without peripheral lesions (n = 46)	Eyes with peripheral lesions (n = 74)	p*
Age (year)	15.13 ± 1.67	14.95 ± 1.56	0.541
Spherical error (D)	-7.31 ± 1.39	-7.80 ± 1.82	0.122
Cylindrical error (D)	-1.46 ± 0.95	-1.69 ± 0.90	0.199
Corneal astigmatism (D)	-1.68 ± 0.78	-1.89 ± 0.65	0.121
SER (D)	-8.04 ± 1.47	-8.64 ± 1.97	0.078
Axial length (mm)	26.67 ± 0.87	27.06 ± 0.86	0.016
IOP (mmHg)	16.91 ± 2.55	15.97 ± 2.50	0.049
Myopia progression rate (D/year)	-0.90 ± 0.24	-0.95 ± 0.27	0.300
Onset of myopia (year)	6.65 ± 1.55	6.47 ± 1.50	0.531

*Unpaired t-test, n = 120

Since lattice degeneration is one of the most common retinal lesion and one with a potential of developing retinal holes and a risk factor of retinal detachment (Lewis, 2003), it is an important retinal lesion to be investigated. Snail track

degeneration is one of the morphologic descriptive terms of lattice degeneration and is counted in the same category in the international classification of disease (i.e. ICD-9). In our study, there were 4 eyes (3.2%) with lattice degeneration 3 eyes (2.5%) with snail track degenerations. Comparisons were made between the eyes with and without lattice degenerations (including snail track degenerations) for subject's age, years of having myopia, age of onset of myopia, myopia progression rate, and intra-ocular pressure. Significant differences were observed in the SER, spherical error, the age of onset of myopia in eyes with and without lattice degenerations (Table 5.6-10). Eyes with lattice degeneration had less myopia and later onset of myopia.

Table 5.6-10 Mean values of parameters in eyes with and without lattice degenerations

Parameters	Eyes without lattice degeneration (n = 113)	Eyes with lattice degeneration (n = 7)	p*
Age (year)	14.98 ± 1.63	15.57 ± 0.79	0.346
Spherical error (D)#	-7.68 ± 1.70	-6.51 ± 0.36	0.000
Cylindrical error (D)	-1.61 ± 0.93	-1.44 ± 0.75	0.643
Corneal astigmatism (D)	-1.81 ± 0.72	-1.76 ± 0.58	0.856
SER (D)#	-8.48 ± 1.84	-7.24 ± 0.58	0.000
Axial length (mm)#	26.92 ± 0.90	26.66 ± 0.39	0.147
IOP (mmHg)	16.25 ± 2.56	17.63 ± 2.19	0.166
Myopia progression rate (D/year)	-0.94 ± 0.26	-0.87 ± 0.17	0.511
Onset of myopia (year)	6.46 ± 1.51	7.86 ± 0.69	0.017

* Unpaired t-test, n = 120

Unequal variance noted in Levene's test for equal variance, equal variance is not assumed

WWOP is also a common retinal lesion found in our study. Comparisons were also made between the eyes with and without WWOP for subject's age, SER, years of having myopia, age of onset of myopia, myopia progression rate and intra-ocular pressure. Eyes with WWOP had more myopia and SER than eyes without WWOP (Table 5.6-11).

Table 5.6-11 Mean values of parameters in eyes with and without WWOP

Parameters	Eyes without WWOP (n = 58)	Eyes with WWOP (n = 62)	p*
Age (year)	15.14 ± 1.55	14.90 ± 1.65	0.424
Spherical error (D)#	-7.28 ± 1.34	-7.92 ± 1.90	0.034
Cylindrical error (D)	-1.53 ± 1.03	-1.67 ± 0.82	0.409
Corneal astigmatism (D)	-1.69 ± 0.77	-1.92 ± 0.63	0.071
SER (D)#	-8.04 ± 1.45	-8.75 ± 2.05	0.030
Axial length (mm)	26.77 ± 0.92	27.04 ± 0.83	0.093
IOP (mmHg)	16.61 ± 2.61	16.01 ± 2.48	0.154
Myopia progression rate (D/year)	-0.91± 0.24	-0.96 ± 0.27	0.266
Onset of myopia (year)	6.72 ± 1.55	6.37 ± 1.47	0.204

* Unpaired t-test, n = 120

Unequal variance noted in Levene's test for equal variance, equal variance is not assumed

As one of the common retinal lesion observed in our study, comparisons were also made between eyes with and without optic nerve crescent (Table 5.6-12).

Eyes with optic nerve crescent had longer axial length (unpaired t-test, p = 0.02), while subject's age, gender, SER, years of having myopia, age of onset of myopia, myopia progression rate, and intra-ocular pressure showed insignificant difference (unpaired t-test, p > 0.05).

Table 5.6-12 Mean values of parameters in eyes with and without optic nerve crescent

Parameters	Eyes without optic nerve crescent (n = 57)	Eyes with optic nerve crescent (n = 63)	p*
Age (year)	15.07 ± 1.61	14.97 ± 1.60	0.729
Spherical error (D)#	-7.51 ± 1.61	-7.70 ± 1.74	0.536
Cylindrical error (D)	-1.47 ± 0.91	-1.72 ± 0.93	0.133
Corneal astigmatism (D)	-1.73 ± 0.69	-1.89 ± 0.72	0.223
SER (D)#	-8.24 ± 1.75	-8.56 ± 1.87	0.339
Axial length (mm)	26.71 ± 0.85	27.09 ± 0.88	0.020
IOP (mmHg)	16.36 ± 2.69	16.30 ± 2.45	0.894
Myopia progression rate (D/ year)	-0.92± 0.27	-0.94 ± 0.25	0.683
Onset of myopia (year)	6.61 ± 1.28	6.48 ± 1.71	0.621

* Unpaired t-test, n = 120

5.6.11. Association between retinal lesions and potential risk factors

The analysis of potential risk factors included the consideration of possible relationship between retinal lesions and gender, “pathological myopia” (myopia -8 D or more), family retinal condition history, family history of high myopia, visual symptoms and axial length. Chi-square tests and Fisher’s test were used for statistical analysis.

5.6.11.1. Gender

There was no significant relationship revealed between gender and retinal lesions (Chi-square, p = 0.326), including WWOP (Chi-square, p = 0.470), optic nerve crescent (Chi-square, p = 0.203) and lattice degeneration (Fisher exact test, p = 0.481).

Table 5.6-13 Association of retinal lesions and gender

Lesion	Chi-square	df	P value
Any retinal lesions*	0.965	1	0.326
Any peripheral lesions*	2.710	1	0.100
Optic nerve crescent*	0.522	1	0.470
WWOP*	1.620	1	0.203
Lattice#	-	-	0.481

* Chi-square test

Fisher exact test (2 cells in contingency table had expected count less than 5)

(n = 120)

5.6.11.2. Age of onset of myopia

There was no significant relationship revealed between congenital myopia (i.e. age of onset of myopia 0 - 5 years) and retinal lesions (Fisher exact test, p = 1.000), including peripheral retinal lesion (Fisher exact test, p = 1.000), WWOP (Fisher exact test, p = 0.811), optic nerve crescent (Fisher exact test, p = 0.229) and lattice degeneration (Fisher exact test, p = 0.352) (Table 5.6-14).

Table 5.6-14 Association of retinal lesions and age of onset of myopia

Lesion	P value
Any retinal lesions	1.000
Any peripheral lesions	1.000
Optic nerve crescent	0.229
WWOP	0.811
Lattice#	0.352

Fisher exact test (2 cells in contingency table had expected count less than 5) (n = 120)

5.6.11.3.Family retinal problem history

There was no relationship found between family retinal problem history and retinal lesions, including the overall retinal lesions (Fisher exact test, p = 0.568), WWOP (Fisher exact test, p = 0.096), and lattice degeneration (Fisher exact test, p = 0.167).

Table 5.6-15 Association of retinal lesions and family retinal problem history

Lesion	Chi-square	df	P value
Any retinal lesions#	-	-	0.568
Any peripheral lesions*	1.484	1	0.223
Optic nerve crescent*	0.235	1	0.628
WWOP#	-	-	0.096
Lattice#	-	-	0.167

* Chi-square test

Fisher exact test (1 cell in contingency table had expected count less than 5)

(n = 120)

5.6.11.4.Family history of high myopia

The relationship between family history of high myopia and retinal lesions was significant (Chi-square = 3.961, p = 0.047, df = 1). A significant relationship was also found between optic nerve crescent and family history of high myopia (chi-square = 4.684, p = 0.030, df = 1). However, no relationship was observed in family history of high myopia and WWOP (chi-square, p = 0.655) and lattice degeneration (chi-square, p = 0.416).

Table 5.6-16 Association of retinal lesions and family history of high myopia

Lesion	Chi-square	df	P value
Any retinal lesions*	3.961	1	0.047
Any peripheral lesions*	0.288	1	0.592
Optic nerve crescent*	4.684	1	0.030
WWOP*	0.200	1	0.655
Lattice#	-	-	0.416

* Chi-square test

Fisher exact test (1 cell in contingency table had expected count less than 5)

(n = 120)

5.6.11.5. Myopia of -8 D or more

There is definition of pathologic myopia in which myopia of -8 D or more has been reported to have higher frequency of ocular complications (Tokoro, 1998). In our study, there was no relationship found between SER more negative than -8 D and overall retinal lesions (chi-square, p = 0.255), peripheral lesions (chi-square, p = 0.401), optic nerve crescent (chi-square, p = 0.351), WWOP (chi-square, p = 0.457) and lattice degeneration (Fisher exact test, p = 0.068). (Table 5.6-17)

Table 5.6-17 Association of retinal lesions and SER -8 D or more

Lesion	Chi-square	df	P value
Any retinal lesions*	1.295	1	0.255
Any peripheral lesions*	0.704	1	0.401
Optic nerve crescent*	0.870	1	0.351
WWOP*	0.552	1	0.457
Lattice#	-	-	0.068

* Chi-square test

Fisher exact test (1 cell in contingency table had expected count less than 5)

(n = 120)

5.6.11.6. Visual symptoms

No significant relationship was found between flashes and the occurrence of retinal lesions (Table 5.6-18). An insignificant relationship has also been observed between floaters and retinal lesions (Table 5.6-19). The results for lattice degeneration and WWOP were also insignificant.

Table 5.6-18 Association of retinal lesions and flashes

Lesion	P value*
Any retinal lesions	0.612
Any peripheral lesions	0.622
Optic nerve crescent	0.726
WWOP	0.232
Lattice	0.114

* Fisher exact test, n = 120

Table 5.6-19 Association of retinal lesions and floaters

Lesion	Chi-square	df	P value
Any retinal lesions*	0.006	1	0.941
Any peripheral lesions*	0.481	1	0.488
Optic nerve crescent*	0.470	1	0.493
WWOP*	0.151	1	0.698
Lattice#	-	-	0.622

* Chi-square test

Fisher exact test (1 cell in contingency table had expected count less than 5) (n = 120)

5.6.11.7. Axial length

There was a significant relationship between axial length and the occurrence of retinal lesions. Eyes with axial length longer than 26.5 mm had a significantly higher chance of having retinal lesions (chi-square = 4.634, p = 0.037, df = 1), optic nerve crescent (chi-square = 6.386, p = 0.019, df = 1) and WWOP (chi-square = 5.753, p = 0.020, df = 1). There was no significant relationship observed between axial length longer than 26.5 mm and lattice degeneration (chi-square = 0.052, p = 1.000, df = 1).

Table 5.6-20 Association of retinal lesions and axial length greater than 26.5 mm

Lesion	Chi-square	df	P value
Any retinal lesions	4.634	1	0.037
Any peripheral lesions	7.987	1	0.005
Optic nerve crescent	6.386	1	0.019
WWOP	5.753	1	0.020
Lattice	0.052	1	1.000

(n = 120)

5.6.12. Investigation on potential risk factors for myopic related retinal changes using binary logistic regression

Apart from simple analyses of individual items, a further analysis by grouping potential risk factors was carried out. Logistic regression estimates were made for the association between retinal lesions and pathological myopia (-8 D or more), axial length for high myopia (26.5 mm or more), age, gender, number of years of having myopia, family retinal history and IOP. Axial length for high myopia was found to be the significant risk factor among different retinal lesions including peripheral lesions, optic nerve crescent and WWOP. The binary logistic regression for axial length was marginally insignificant ($p = 0.074$) for "any retinal lesions". Other potential risk factors were statistically insignificant, except for the estimate of family retinal history in WWOP (Table 5.6-21).

Table 5.6-21 Odd ratios in binary logistic regression for various potential risk factors among different retinal lesions

Potential risk factors	Any retinal lesions	Any peripheral lesions	Optic nerve crescent	WWOP	Lattice
Pathological myopia (≤-8 D)	1.936	1.234	1.270	1.008	0.178
Axial length for high myopia (≥ 26.5 mm)	2.489	3.369**	2.798*	2.930*	1.443
Age	1.182	0.939	1.002	0.830	1.915
Gender	1.381	1.358	1.058	1.095	0.833
No. of years having myopia	0.849	1.035	1.009	1.212	0.505
Family retinal history	1.525	3.099	1.941	4.495*	0.126
IOP	0.940	0.858	0.992	0.892	1.220

* p value less than 0.05

** p value less than 0.01

5.7. Discussion

This study aims to determine the prevalence of myopic related retinal changes in older schoolchildren in the Chinese community. We recruited subjects in the community by newspaper advertisements, letter to secondary schools, posters and leaflets. However, a self-selection bias cannot be eliminated. The subjects needed to call in to join the study and come with their parents. Most of the subjects never had a dilated fundus examination before. However, this information was not included in the questionnaire. It would have been beneficial to estimate and include eye health awareness of the subjects.

5.7.1. Prevalence of high myopia related retinal changes

The mean age of boys was older than the girls and they had longer mean axial lengths, but no significant difference in refractive error was observed. Interestingly, boys did not have a greater chance of having retinal lesions despite the fact that their mean axial eye length was longer, even in our age-matched analysis. In the boys-and-girls-combined analysis, we observed that peripheral retinal lesions were correlated with longer axial length. These findings might

indicate gender was not a determining risk factor for the retinal lesions in the 12 - 18 age population.

There are reports on the prevalence of myopic related retinal degenerations (Hyams and Neumann, 1969, Curtin and Karlin, 1971, Kirker and McDonald, 1971, Celorio and Pruett, 1991, Pierro *et al.*, 1992, Ho *et al.*, 1994, Gozum *et al.*, 1997, Lam *et al.*, 2005, Lai *et al.*, 2008). Those reports used either clinic-based or population-based samples, with predominantly adult subjects and with a broad range of age. Since age might be a factor influencing the occurrence of degeneration, it is difficult to explore how early high myopia affects the retina from reviewing those reports. Therefore, in our study, teenagers were studied to determine myopic related retinal changes.

Our study showed lower prevalence of retinal lesions as compared with previous results examining adult population. Since lattice degeneration may occur in early age and peak at the second decade of life (Lewis, 2003), the prevalence of lattice degeneration was lower in our subjects as compared with Lam *et al.* (2005). The results for prevalence of lattice degeneration reinforce the importance of dilated fundus examination in high myopic adolescents (12 to 18 years old). In some

high myopic subjects, retinal degeneration starts in the first decade of life. To our surprise, our study showed that eyes with lattice degeneration had lower myopia than those eyes without lattice degeneration, and had later age onset of myopia. The statistical significance may be related to the small number of lattice degeneration cases found in our samples (7 cases comprising 5.8% of total cases), leading to unequal variance between groups under t-test comparison as shown by the Levene's test, and a significance shown by chance.

The prevalence of WWOP in our study was greater than some local studies of adult populations (mean age 33.5 and 36 years) (Lam *et al.*, 2005, Lai *et al.*, 2008). Our results were comparable with Ho *et al.* (1994), who recruited high myopic college students in Taiwan. Is the prevalence of WWOP higher in younger high myopes? Or has it changed recently? No doubt this will be an interesting topic for further investigation.

5.7.2. Possible risk factors

Our study tested many possible risk factors for the association between retinal lesions and age, gender, family retinal problem history, age onset of myopia,

myopia progression rate, number of years of having myopia, myopia -8 D and over, intraocular pressure, and visual symptoms of flashes and floaters. However, none of these showed significance in our results. The degenerative effect caused by aging might not be significant for adolescents (12 - 18 years). We found that a bigger eye with axial length longer than 26.5 mm would have a higher risk of having retinal lesions, but it is independent as to gender, despite the fact that the eyes of boys are bigger than that of girls.

Our results showed no significant association between retinal lesion and family retinal problem history. Although retinal lesions like retinal detachment, was found to be genetically associated (Go *et al.*, 2005, Mitry *et al.*, 2011), there was no retinal detachment indentified in our analysed samples. While there might be no genetic association in other retinal lesions such as lattice degeneration and WWOP, our analysis showed that family retinal problem history is not a risk factor for myopic related retinal changes.

Early onset of myopia did not lead to a greater chance of retinal lesion, as found in our study. There was no significant difference in myopia progression rate and number of years of having myopia between eyes with and without retinal lesions.

Besides, myopia -8 D and over, intraocular pressure, and visual symptoms of flashes and floaters were not risk factors of retinal lesions in our study. None of these has a direct influence on eye growth, and thus the effect exerted on the chance of getting retinal changes is insignificant.

There was a significant relationship between axial length and retinal lesions, including “any peripheral retinal lesions”, white-without-pressure and optic nerve crescent, but not lattice degeneration. The largest eye in our study had an axial length of 29.44 mm, but the mean axial length of the eyes with lattice degeneration (including snail track degeneration) was 26.66 ± 0.39 mm. This finding partly agrees with previous report by Pierro *et al.* (1992), who showed a the positive correlation between axial length and the presence of white-without-pressure, lattice degeneration and paving stone degeneration. Besides, they observed no significance between axial length and retinal detachment, retinal holes, and peripheral pigment. Celorio and Pruett (1991) reported that the highest prevalence of lattice degeneration was among myopic eyes of axial length 26.0 mm to 26.9 mm, and found that the lowest prevalence of lattice degeneration was found among eyes of axial length 32 mm or greater. Lam *et al*. (2005) also pointed out that a difference in axial length could not be

demonstrated between eyes with and without lattice degeneration. Perhaps axial length is not a determining risk factor for the occurrence of lattice degeneration in the age group of 12 - 18, but this observation should not be generalized to other age groups, since a difference in age spectrum might also influence the occurrence of retinal degenerations.

We found that the eyes of boys had longer axial lengths than girls but there was no significant difference in SER and myopia between boys and girls. Based on the observation that longer axial lengths were found in eyes with retinal lesions and WWOP, it might be expected that boys would have more retinal lesions and WWOP than girls. However, a chi-square test showed no significance in the occurrence of retinal lesions and WWOP between boys and girls. This may be due to the difference in the mean age of boys and girls. Girls were significantly younger than boys in our study. Hence, we suggest that the age may play a role in the occurrence of retinal lesions during adolescence, though there was no other evidence to support this.

The most common retinal lesion found in our study was optic nerve crescent (Table 5.6-3). There was a significant relationship between family history of high

myopia and the occurrence of optic nerve crescent (Table 5.6-16). Eyes with optic nerve crescent were also found to be having longer axial length (Table 5.6-12). Perhaps the more myopic and larger eyes, are more likely to have optic nerve crescent. Nakazawa *et al.* (2008) reported that the formation of optic nerve crescent was associated with myopia progression in mild and moderate myopia cases. In our study, the relationship between myopia progression rate and occurrence of optic nerve crescent could not be demonstrated.

Tokoro (1998) stated that myopia of -8 D or more at age 6 or above would be pathologic. Our results failed to show the association between myopia of -8 D or more and retinal complications. Interestingly, we found that eyes with axial length exceeded 26.5 mm would have high frequency of any retinal lesions and peripheral retinal lesions. Perhaps this is a risk factor for determining the chance of having retinal lesions. We suggest that axial length measurement in high myopic patients should be monitored, not only for myopia progression, but also for prediction of the risk of retinal lesions.

5.7.3. Possible bias and limitations

Since our study required subjects to join in by themselves, self-selection bias might exist. We tried to minimise the self-selection bias by various subject recruitment methods, including newspaper advertisement, letter to schools, leaflets and posters. One of the sources of self-selection bias might come from the observation of visual symptoms including flashes and floaters. In our results, the possible bias effect caused by symptomatic subjects was not evident. There were only 2 subjects who experienced flashes symptoms, and no significant association was found between flashes and floaters and the occurrence of retinal lesions.

In our sample size calculations, we adopted the following formula (Daniel, 1999):

$$\mathrm{N} \geq \frac{Z^2 P(1-P)}{W^2}$$

Where N is sample size, Z is the standardized score related to the level of confidence (now chosen as 1.96), P is the proportion of cases with a particular attribute in the population, and W is the confidence interval assumed to be 0.05. Lam *et al.*(2005) found the prevalence of lattice degeneration was 12.2% in adult

population. We expect a lower percentage in younger group, say 8%. Based on the above assumption, this is now applied to equation, with Z = 1.96, P = 0.08, W = 0.05.

$$N \geq \frac{1.96^2 0.08(1-0.08)}{0.05^2}$$

Then, N = 113.

Our samples size was 120 subjects, which was greater than our minimal calculated sample size, and the prevalence of lattice degeneration found in our study was 5.8%, which was lower than what we assumed in the sample size calculation.

5.8. Conclusions

Peripheral retinal degenerative lesions and optic nerve crescent were found in a significant proportion of high myopic teenage subjects. The results showed that the prevalence of lattice degeneration among 12 - 18 year-old high myopia schoolchildren was lower than the prevalence for adult high myopic population, as previously reported. There was a positive relationship between axial length and peripheral retinal lesions. There is a higher chance of having retinal lesions in eyes with axial length exceeding 26.5 mm in the ages between 12 - 18 years. No significant association was found between retinal lesions and age, gender, family retinal problem history, age onset of myopia, myopia progression rate, number of years of having myopia, myopia -8 D and over, intraocular pressure, and visual symptoms of flashes and floaters.

6. Chapter Six. Retinal thickness profile among Hong Kong Chinese high myopes

This study has been published in 2010:

Cheng, S. C., Lam, C. S. and Yap, M. K.(2010). Retinal Thickness in Myopic and Non-myopic Eyes. *Ophthalmic Physiol Opt* **30**, 776-784.

6.1. Introduction

The enlargement of the eyeball is associated with myopia progression and studies have suggested that the enlargement of the eyeball may result in thinning and degenerative changes of the retina (Pierro *et al.*, 1992) and therefore retinal thickness changes may reflect changes in myopic related retinal degenerative changes. With the advent of modern imaging technologies such as optical coherence tomography (OCT) and retinal thickness analyzer (RTA), it is now possible to study retinal thickness *in vivo*.

Clinical methods of estimating retinal thickness could include slitlamp biomicroscopy and stereophotography. However, these methods only provide a subjective evaluation of retinal thickness. In order to provide an evidence-based

diagnosis and precise monitoring of retinal thickness changes, quantitative measurement of the retinal thickness is indicated. As technology advances, optical coherence tomography (OCT) is one of the methods that makes *in vivo* noninvasive retinal thickness measurements available (Huang *et al.*, 1991, Hee *et al.*, 1995), and it offers different scanning protocols for the central retinal region. The Stratus OCT (Carl Zeiss Meditec, Dublin, CA) is a computerized precision optical instrument which uses the low-coherence interferometry principle that generates cross sectional images of the retina with equal or less than 10 microns axial resolution. The interferometer uses a broad bandwidth near-infrared light beam (820 nm) as a signal source, which projects onto the retina to resolve retinal structures. It measures the echo delay time of light which is reflected and then backscattered from different retinal structures. This echo time delay of light reflected from the retina is then compared with another echo time delay, which is from the same light beam but reflected from a reference mirror at known distances. An interference phenomenon occurs when the instrument combines the above two reflected light pulses, and this is measured by a photo-detector inside the Stratus OCT.

Early investigations of retinal thickness in myopia were mainly focused on the macula region. Earlier studies using first and second generation OCT found that retinal thickness was not related with myopia (Wakitani *et al.*, 2003, Lim *et al.*, 2005). However, more recent studies using the Stratus OCT have reported that increasing axial myopia is associated with reduced macular retinal thickness (Luo *et al.*, 2006, Lam *et al.*, 2007). Higher resolution and a shorter scanning time of the newer OCT and a more detailed analysis of the data were offered as reasons to explain the new findings.

Whereas the macula may be thinner in the myopic eye, it is unclear whether the peripheral retina of the myopic eye follows a similar pattern. Chujo *et al.* (1983) measured retinal thickness in five high myopic eyes (-8 D to -12 D) at the mid-posterior region between the temporal equator and fovea, using A-scan ultrasonography. They reported that the retinal thickness was 116.2 ± 7.6 μm, and stated that it was thinner than those of the normal eye.

OCT has been reported to yield repeatable and reproducible retinal thickness measurements for both macular and optic disc areas (Koozekanani *et al.*, 2000, Jones *et al.*, 2001, Massin *et al.*, 2001, Muscat *et al.*, 2002, Browning and Fraser,

2004, Paunescu *et al.*, 2004). By applying the appropriate scanning protocol for peripheral retina, it may be feasible to measure peripheral retinal thickness in human eyes *in vivo* in a repeatable manner. Thus, the profile of the retina and peripheral retinal thickness can be investigated.

The prevalence of peripheral retinal changes such as white without pressure, lattice degeneration, pigmentary and paving-stone degeneration and retinal breaks was found to have significant correlation with a longer axial length in Western (non-Asian) studies (Pierro *et al.*, 1992, Yura, 1998). Since axial elongation may cause mechanical stretching and thinning of the choroid and retina, it may associated with degenerative changes (Pierro *et al.*, 1992) and peripheral retinal thickness might be a possible risk factor for peripheral retinal changes.

6.2. Objectives

The purpose of this study is to investigate whether there is a change in peripheral retinal thickness when the eye is distended, and to explore whether peripheral retinal thickness is a potential risk factor indicating peripheral retinal lesions.

6.3. Methods

In this section, the details in equipment, subject recruitment, OCT experiment setup, reliability with our own modification for eccentric fixation, and statistical analysis would be described.

6.3.1. Subjects

Young adults (age 18 - 30 years) were recruited and categorized into two groups, myopic group (SER -6 D to -14 D) and non-myopic group (SER +3 D to -0.5 D). All subjects underwent an eye examination at the Optometry Clinic of the Hong Kong Polytechnic University. This included a visual acuity test, refraction, non-contact tonometry, visual field assessment and a dilated fundus examination. During fundus examination, the following were recorded as “retinal lesions”: lattice degeneration, white-without-pressure, microcystoid degeneration, chorioretinal atrophy, pigmentary change, retinal hole and retinal break. For all subjects, the data from one eye only was used in this study. By default, this was the right eye, unless it did not meet the inclusion criteria in which case the left eye was used. All eyes selected were free from amblyopia, disease, surgery,

medication, or trauma. Each eye had best-corrected visual acuity better than 6/9 on a Snellen chart. Informed consent was obtained from each subject. Our study followed the tenets of the Declaration of Helsinki and was approved by the Human Subjects Ethics Sub-committee of The Hong Kong Polytechnic University.

6.3.2. Refractive status and axial length measurement

Refractive status was determined using an open-field autorefractor (Shin-Nippon SRW-5000, Japan). Prior to measurement, one drop of 0.4% Novesin followed by two drops of 1% Tropicamide instilled five minutes apart (Owens *et al.*, 1998, Siderov and Nurse, 2005) were administered. Thirty minutes after administration of the eyedrops, ten autorefractor readings were taken and averaged. Axial length was measured using the IOL Master (Carl Zeiss Meditec, Dublin, CA).The mean of five measurements was taken.

6.3.3. OCT experimental set up

Retinal thickness was measured using the StratusOCT (model 3000, software ver.4.0; Carl Zeiss Meditec, Dublin, CA). Three measurements were taken with short breaks between each measurement. The fellow eye was occluded during measurement. The measurement of the macular area was performed with the Macular Thickness Map scanning protocol. To determine the horizontal retinal thickness profile, the Customized Line Scan protocol was used with a scan length of 3 mm and 512 A-scans vertically. Two external fixation lights (LEDs) were positioned at 40-degrees horizontally on either side of the instrument to enable peripheral measurements to be made (Figure 6.3-1 and Figure 6.3-2).

The vertical positions of the LEDs were at the same level as the canthus marks on the headrest of the instrument. This external fixation device was mounted on a rail which allowed the device to be adjustable for horizontal alignment with the subject's eye. The subject was instructed to fixate at the internal target for Macular Thickness Map and 10, 20, and 26 degrees nasal and temporal retina measurements, and external mounted LEDs for peripheral retina scan at 40-degree eccentricity. All measurements were collected by the same

investigator (SC). Measurements were obtained with signal strengths not less than 7. Measurements of retinal thickness were the average of three separate scans for the same location. Readings in horizontal retinal thickness profiles were extracted from each scan result at the 256th acquisition point, which is the mid-point of the total 512 A-scan points of each OCT measurement.

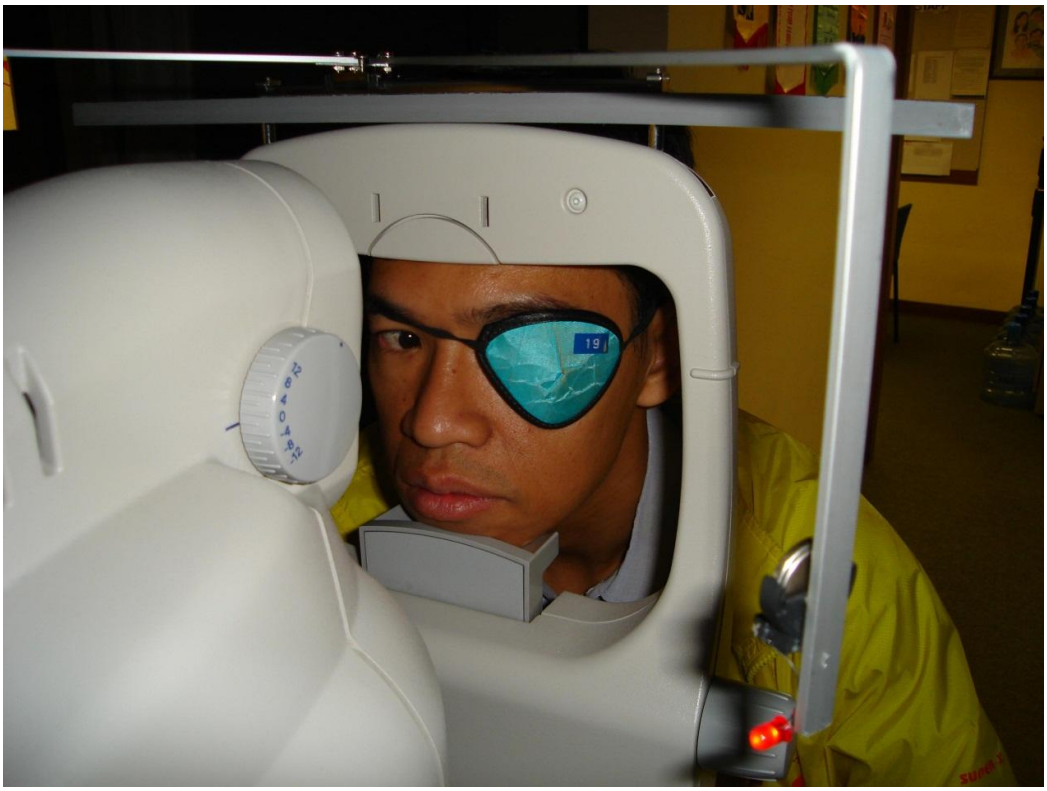


Figure 6.3-1 OCT experimental set up

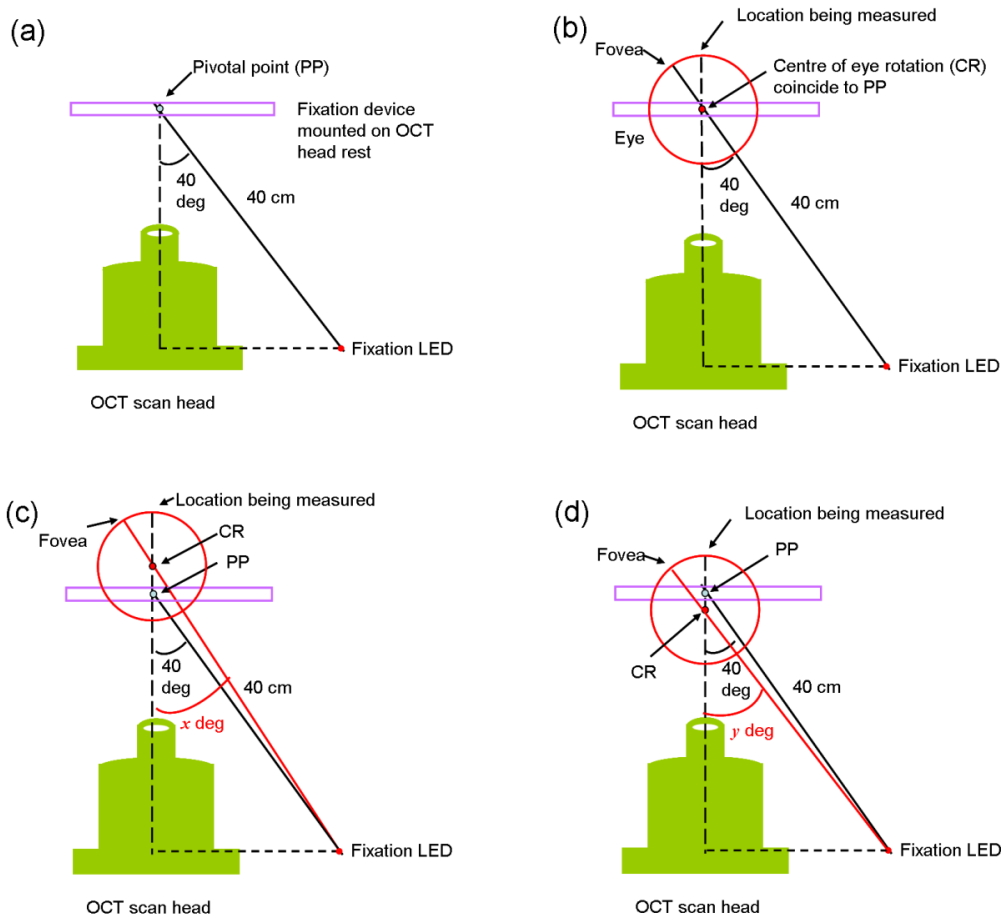


Figure 6.3-2 Schematic diagram of experimental setup of the external fixation target.

(a) The pivotal point (PP) could be horizontally adjusted and was the designated point to coincide to the centre of eye rotation (CR), thus (b) the visual axis of the subject's eye would be aligned correctly. However, there was a possible error caused by relative positioning of CR with PP. Since there might be variation of the location of CR between subjects, (c) and (d) show the possible error in measuring angle due to CR not being coincident with PP. Either CR was (c) behind PP, or (d) beyond PP. This would cause an error in measuring angle [angle x (shown in c) or y (shown in d)].

6.3.4. Repeatability test of OCT in measuring peripheral retinal thickness and measurement of retinal profile

Prior to analysis of the relationship between retinal thickness and myopia, a repeatability study was conducted for peripheral retinal thickness measurements. A Bland-Altman (Bland and Altman, 1986) analysis showed that good repeatability of peripheral retinal thickness measurements can be achieved. Figure 6.3-3 and Figure 6.3-4 show as a sample that conducted in this study. The mean differences of the retinal thickness measured at various eccentricities ranged from -0.43 to 2.59 μm. The 95% confidence limits were around ± 14 μm except at the 20-degree nasal retina (± 22.80 μm). The 20-degree nasal retina was near the optic disc margin which had a greater variation in thickness. Thus, a subtle change in retinal scanning location might cause a big difference in retinal thickness.

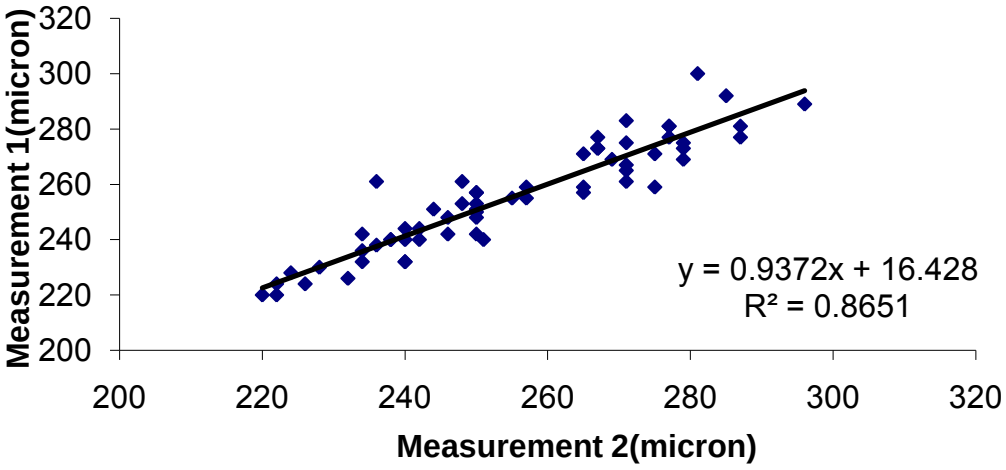


Figure 6.3-3 Scattergram of test-retest of retinal thickness measurement setup for 10 degree nasal location

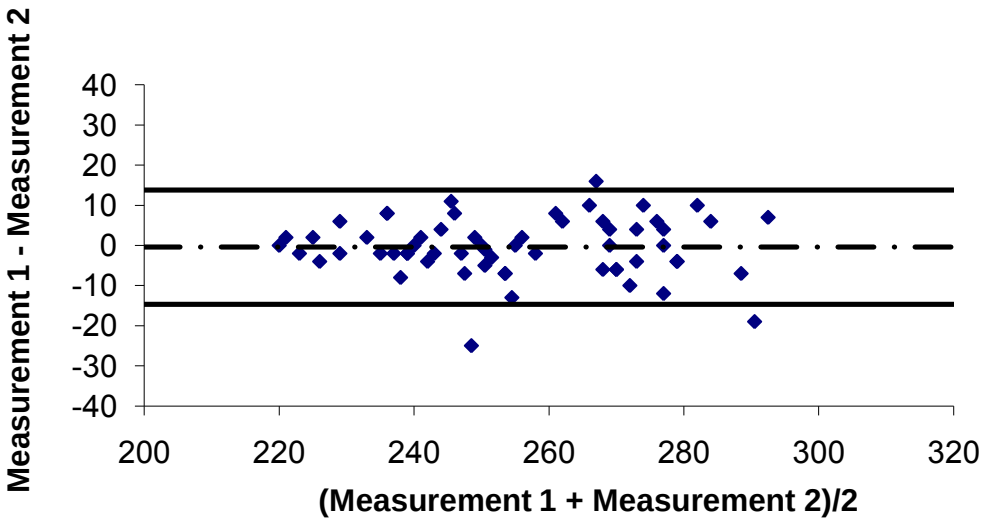


Figure 6.3-4 Agreement for the retinal thickness measured by OCT measured in two measurements 10 degree nasal location

6.3.5. Statistical Analysis

All data were analyzed using SPSS (SPSS Inc, Chicago, IL), and statistical significance was assumed at the $p < 0.05$ level. Descriptive statistics and analysis of variance (ANOVA) were performed. The potential association of retinal thickness change across the retinal profile and the change in axial length was investigated.

6.4. Results

Sixty-one eyes from sixty-one Hong Kong Chinese subjects were used, comprising 30 myopic eyes and 31 non-myopic eyes. The mean age of the myopic and non-myopic groups were 22.73 years and 23.26 years respectively ($p = 0.504$, unpaired t-test). The percentage of male participants was 43.3% and 32% in the myopic and non-myopic groups, respectively ($p = 0.434$, Fisher's test). The mean axial length in the myopic group was 26.66 ± 1.11 mm and 23.69 ± 0.71 mm in the non-myopic group ($p < 0.0001$, unpaired t-test). The SER was -7.88 ± 1.82 D (ranged from -6.00 D to -13.63 D) and +0.44 ± 0.69 D (ranged from +2.75 D to -0.50 D) in myopic and non-myopic group respectively ($p <$

0.0001, unpaired t-test). Axial length was well correlated with the SER (Pearson's correlation, $p < 0.001$, $r = -0.918$).

6.4.1. Macular thickness

From the Macular Thickness Maps, macular thickness ranged from 162 μm to 271 μm in the myopic group (Table 6.4-1 and Figure 6.4-1). In the non-myopic group, macular thickness ranged from 149 μm to 281 μm. The inner nasal quadrant was the thickest part of the macula in both subject groups. At foveal minimum and fovea, the myopic group had a thicker retina than the non-myopic group ($p = 0.002$ and 0.044 respectively). At other zones, retinal thickness was significantly thinner in the myopic group than in the non-myopic group ($p < 0.01$, unpaired t-test).

Table 6.4-1 Comparison of central retinal thickness between non-myopic and myopic eyes among various retinal zones

	Mean (μm)		p*
	Non-myopic (n = 31)	Myopic (n = 30)	
Foveal minimum	149 ± 11.80	162 ± 19.21	0.002
Fovea	191 ± 12.37	199 ± 17.27	0.044
Temporal inner	264 ± 10.15	255 ± 14.04	0.008
Superior inner	280 ± 10.84	268 ± 12.83	0.000
Nasal inner	281 ± 9.63	271 ± 13.73	0.001
Inferior inner	278 ± 9.65	267 ± 13.80	0.001
Temporal outer	233 ± 9.29	215 ± 13.20	0.000
Superior outer	253 ± 11.79	236 ± 15.17	0.000
Nasal outer	269 ± 13.73	253 ± 16.59	0.000
Inferior outer	242 ± 14.55	221 ± 14.03	0.000

* Unpaired t-test

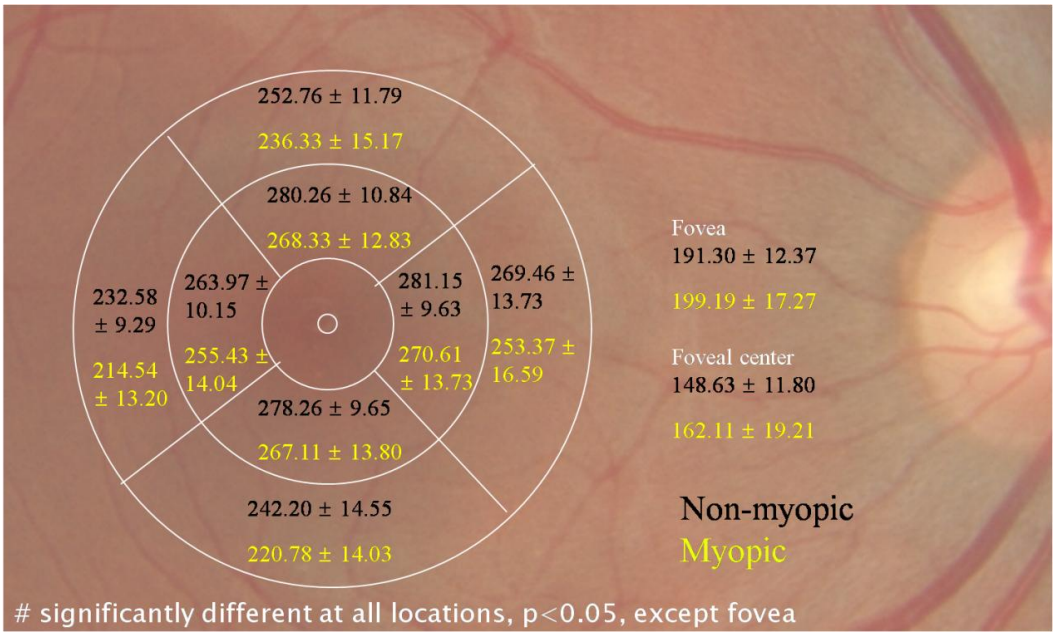


Figure 6.4-1 Retinal thickness among different zones in macular thickness map

6.4.2. Peripheral thickness

Along the central eighty degree horizontal meridian, the retinal thickness profiles of both the myopic and non-myopic groups showed a similar pattern (Figure 6.4-2). Retinal thickness reduced with greater eccentricity both nasally and temporally. The thinnest part of the retina in both groups was at the 40-degree temporal retina with a mean of 124 µm and 134 µm for myopic and non-myopic groups respectively (One-way ANOVA, $p < 0.001$ in both myopic and non-myopic groups, Table 6.4-2).

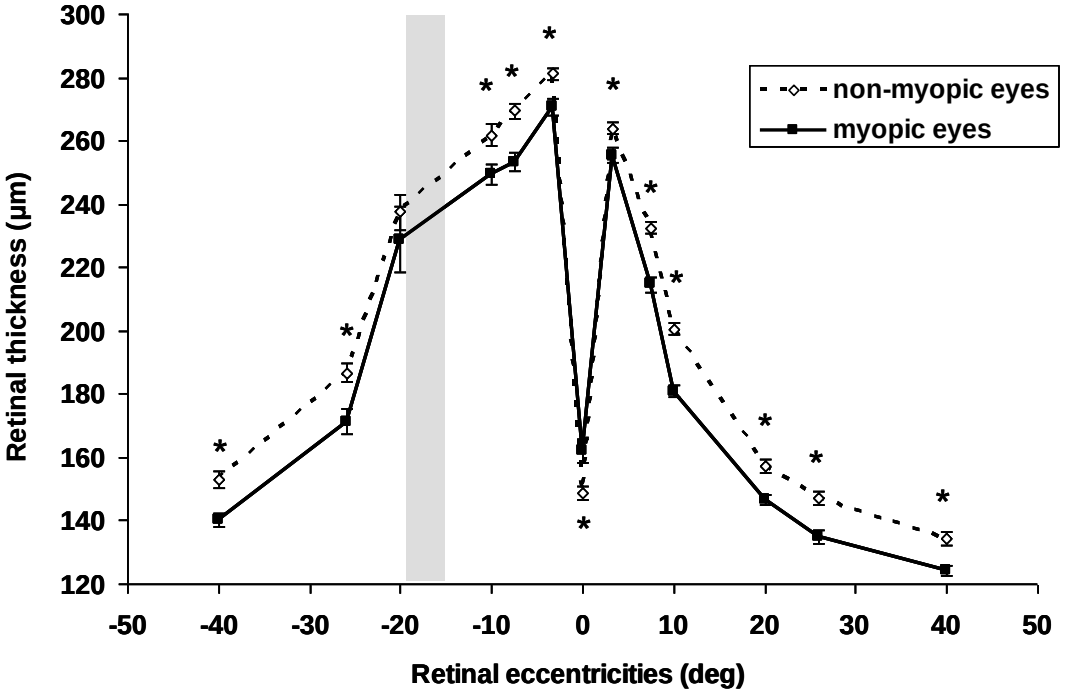


Figure 6.4-2 Retinal thickness profile across the central 80 degrees in myopic and non-myopic eyes

Table 6.4-2 Difference in retinal thickness between myopic and non-myopic eyes from foveal minimum to peripheral retinal locations

Locations	Mean (μm) Myopic (n = 30)*	Mean (μm) Non-myopic (n = 31)*	Thinning of retinal thickness (μm)	Percentage of thinning in high myopes (%)	p†
40 deg nasal	140 ± 12.37	153 ± 14.69	12.71	8.31	0.001
26 deg nasal	171 ± 21.07	187 ± 16.79	15.38	8.24	0.003
20 deg nasal	229 ± 55.94	238 ± 31.58	8.76	3.69	0.453
10 deg nasal	249 ± 17.34	262 ± 18.67	12.67	4.84	0.008
10 deg temporal	181 ± 10.75	201 ± 9.48	19.66	9.80	0.000
20 deg temporal	147 ± 9.66	157 ± 11.37	10.58	6.73	0.000
26 deg temporal	135 ± 10.90	147 ± 11.18	12.25	8.33	0.000
40 deg temporal	124 ± 8.49	134 ± 11.09	10.12	7.53	0.000

* One-way ANOVA with Bonferroni post-hoc test. Significant differences were noted among all retinal eccentricities ($p < 0.05$) in myopic group and in non-myopic group.

† Unpaired t-test for retinal thickness between myopic and non-myopic eyes at corresponding locations.

The retinal thickness findings for different retinal eccentricities are shown in Table 6.4-2. Retinal thickness was significantly lower in the myopic group compared with non-myopic group for all eccentricities ($p < 0.01$, unpaired t-test), except the optic disc region (20-degree nasal retina) ($p = 0.453$).

Peripheral retinal thickness correlated with axial length ($p<0.05$, Table 6.4-3), and refractive error ($p < 0.01$) except at 20-degree nasal retina ($p = 0.234$) which

is near to the optic disc. Peripheral retinal thicknesses decreased with longer axial length and higher degree of myopia.

Table 6.4-3 Difference in retinal thickness between myopic and non-myopic eyes from foveal minimum to peripheral retinal locations

Locations	Mean (μm)		Thinning of retinal thickness (μm)	Percentage of thinning in high myopes (%)	p†
	Myopic (n = 30)*	Non-myopic (n = 31)*			
40 deg nasal	140 ± 12.37	153 ± 14.69	12.71	8.31	0.001
26 deg nasal	171 ± 21.07	187 ± 16.79	15.38	8.24	0.003
20 deg nasal	229 ± 55.94	238 ± 31.58	8.76	3.69	0.453
10 deg nasal	249 ± 17.34	262 ± 18.67	12.67	4.84	0.008
10 deg temporal	181 ± 10.75	201 ± 9.48	19.66	9.80	0.000
20 deg temporal	147 ± 9.66	157 ± 11.37	10.58	6.73	0.000
26 deg temporal	135 ± 10.90	147 ± 11.18	12.25	8.33	0.000
40 deg temporal	124 ± 8.49	134 ± 11.09	10.12	7.53	0.000

* One-way ANOVA with Bonferroni post-hoc test. Significant differences were noted among all retinal eccentricities ($p < 0.05$) in myopic group and in non-myopic group.

† Unpaired t-test for retinal thickness between myopic and non-myopic eyes at corresponding locations.

To determine whether there was an equal amount of thinning along the horizontal retina in myopic eyes, a comparison was made between the retinal thickness at different eccentricities of the nasal and temporal retina. The amount of retinal thinning was defined as the retinal thickness of myopic eyes at a specific eccentricity subtracted from the averaged retinal thickness of non-myopic eyes at the same eccentricity. The average percentage of retinal thinning in the myopic

group among the various peripheral locations was 7.18%. There was no significant difference of retinal thinning across eccentricities along nasal and temporal retina (Two-way ANOVA).

Within the limits of the resolution of the StratusOCT, the retinal image could be divided into two layers, namely the photoreceptor layer (PL) (from retinal pigment epithelium to outer nuclear layer) and the mid-inner retinal layer (ML) (from outer plexiform layer to nerve fibre layer), as previously reported by Wolsey *et al.* (2008) (Figure 6.4-3). With this, we could identify which layer of retina actually has thinned. The values of thickness of the two layers are shown in Table 6.4-4. In general, myopic eyes had a thinner photoreceptor layer at peripheral retinal locations (Figure 6.4-4). Two-way ANOVA shows significant difference for the thickness at different retinal locations and between the two refractive groups for the thickness of PL and ML. A significant main effect was obtained for refractive status in both separated layers, $F = 37.54$, $p < .001$ in PL and $F = 44.67$, $p < .001$ in ML. A significant main effect was also obtained for different retinal locations, $F = 66.41$, $p < .001$ and $F = 300.36$, $p < .001$ in ML and PL respectively. Myopic eyes had significantly thinner photoreceptor retinal thickness at 26 and 40 degree nasal retina, and 20, 26, and 40 degree temporal

retina compared to non-myopic eyes. Myopic eyes also had significantly thinner mid-inner retinal thickness at 10 and 26 degree temporal retina compared to non-myopic eyes.

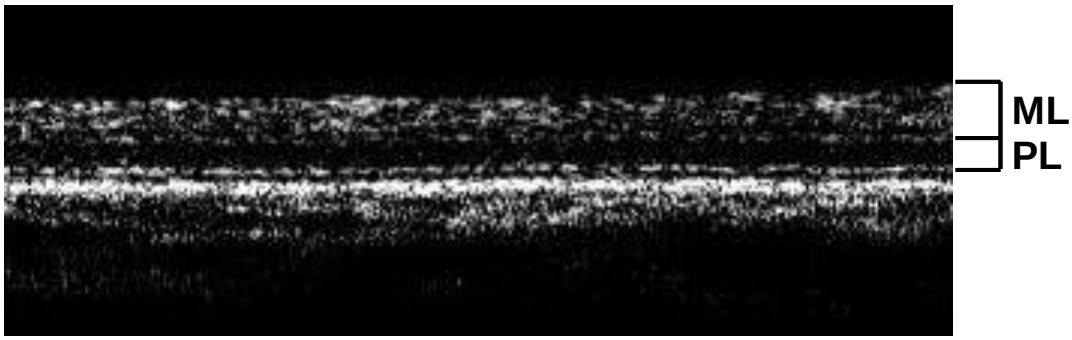


Figure 6.4-3 A sample image from the OCT peripheral retina measurement
Two layers of retina could be visually delineated and measured using the OCT program with manual measurement. Photoreceptor layer (PL) (from the inner boundary of the RPE to the outer boundary of the low reflective band representing the outer plexiform layer) and the mid-inner retinal layer (ML) (from the outer boundary of the outer plexiform layer to the boundary of the nerve fibre layer) were defined as shown.

Table 6.4-4 Retinal thickness among various eccentricities presented in separated layers

	Myopic		Non-myopic	
	PL	ML	PL	ML
10 nasal	74 ± 12.26	176 ± 14.45	77 ± 8.20	185 ± 17.68
10 temporal	74 ± 7.23	115 ± 7.95	78 ± 10.73	134 ± 13.19
20 nasal	89 ± 23.34	144 ± 33.25	86 ± 13.83	157 ± 25.46
20 temporal	62 ± 9.61	94 ± 8.11	70 ± 9.58	100 ± 9.52
26 nasal	64 ± 13.39	114 ± 11.96	76 ± 11.41	118 ± 10.13
26 temporal	54 ± 8.21	90 ± 9.81	62 ± 8.94	96 ± 6.93
40 nasal	50 ± 8.69	96 ± 10.71	58 ± 8.80	103 ± 11.17
40 temporal	48 ± 9.62	83 ± 10.90	58 ± 10.34	87 ± 8.80

PL denoted as Photoreceptor layer (from RPE to outer nuclear layer). ML denoted as mid-inner retinal layer (from outer plexiform layer to nerve fibre layer).

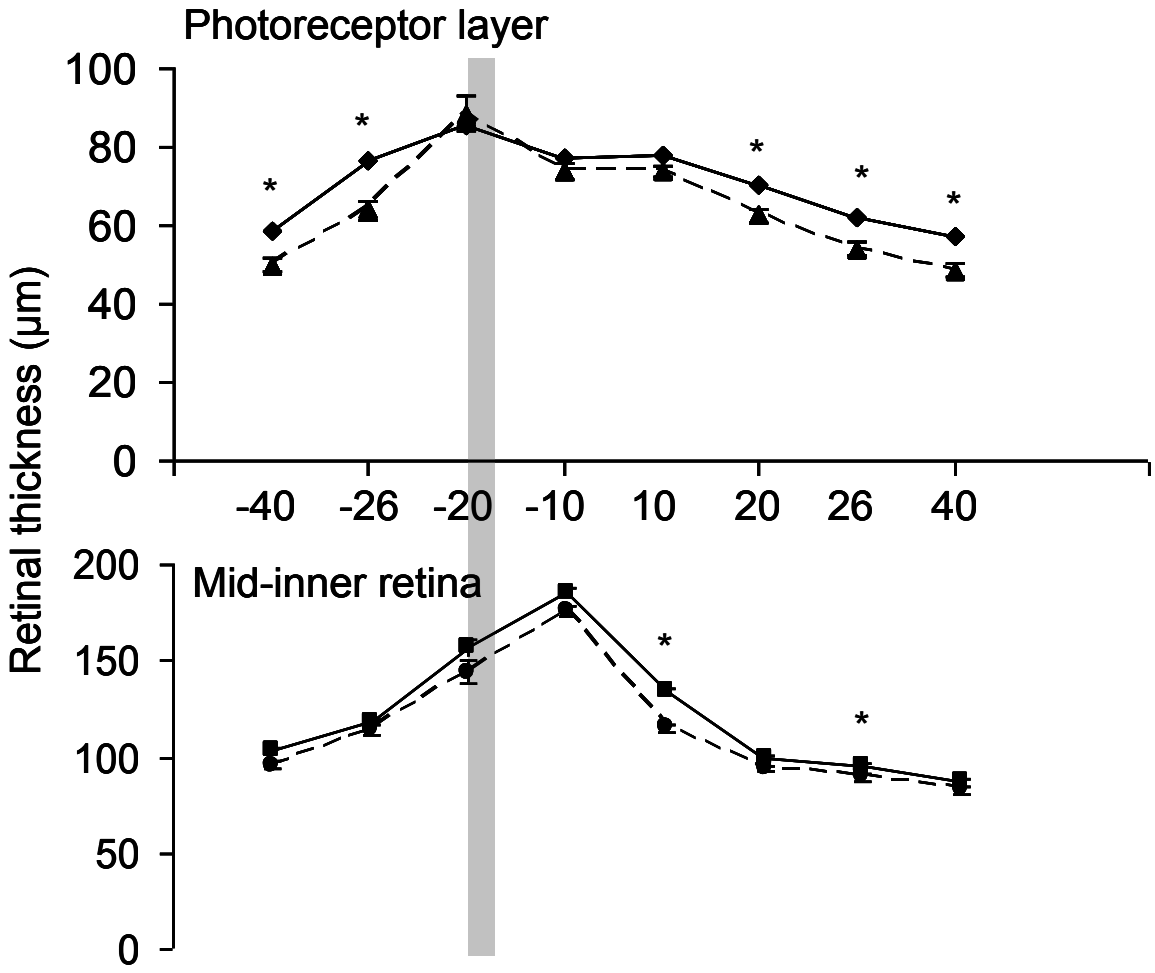


Figure 6.4-4 Retinal thickness presented in separated layers

Horizontal retinal thickness profiles in separated layers across different eccentricities among myopic and non-myopic eyes. Nasal retinal measurements were presented as negative eccentricities. Shaded area corresponds to optic disc area. Values shown represent the mean ± S.E.M. There appeared a general trend that myopic eyes (dashed lines) had thinner photoreceptor retina and mid-inner layer retina than non-myopic eyes (solid lines). Myopic eyes had significantly thinner photoreceptor retinal thickness at 26 and 40 degree nasal retina, and 20, 26, and 40 degree temporal retina than non-myopic eyes. Myopic eyes also had significantly thinner mid-inner retinal thickness at 10 and 26 degree temporal retina than non-myopic eyes. Locations with significant difference in retinal thickness between myopic and non-myopic eyes were marked with an asterisk (*).

At the foveal minimum, the two layers were delineated by separating the total thickness of fovea into the RPE to outer segment layer (OS) and mid-inner retinal layer (ML). The mean thickness of the OS layer was 71.60 ± 4.65 μm in non-myopic eyes and 72.59 ± 3.85 μm in myopic eyes. The difference was not significant ($p = 0.371$). The mean thickness of the ML layer was 115.01 ± 9.47 μm in non-myopic eyes and 125.28 ± 15.39 μm in myopic eyes. Myopic eyes had a significantly thicker ML layer than non-myopic eyes (t-test, $p = 0.003$).

6.4.3. Peripheral thickness and peripheral retinal lesions

Peripheral retinal lesions were detected in 22 eyes during dilated fundus examination in our sample of 61 eyes. The lesions included lattice degeneration (3 eyes), white-without-pressure (17 eyes), microcystoid degeneration (2 eyes), chorioretinal atrophy (2 eyes) and pigmentary hypertrophy (1 eye). Twenty-one out of the 30 myopic eyes (73%) had peripheral retinal lesions while only one out of 31 non-myopic eyes (3%) had a peripheral retinal lesion. Is retinal thickness an important factor associated with the occurrence of peripheral retinal lesions? Within the myopic group, no significant difference in retinal thickness was found between eyes with and without peripheral retinal lesions ($p > 0.05$, unpaired

t-test) (Figure 6.4-5). The one eye in the non-myopic group with peripheral retinal lesion (n = 1) had a retinal thickness of 255.33 µm at 3.33-degree nasal retina compared the group mean of 282.01 ± 8.49 µm (CI: 265.36 µm – 298.66 µm). Within our myopic group, there was no linear relationship between retinal thickness and occurrence of retinal lesions. However, clearly the myopic group had more retinal lesions than the non-myopic group.

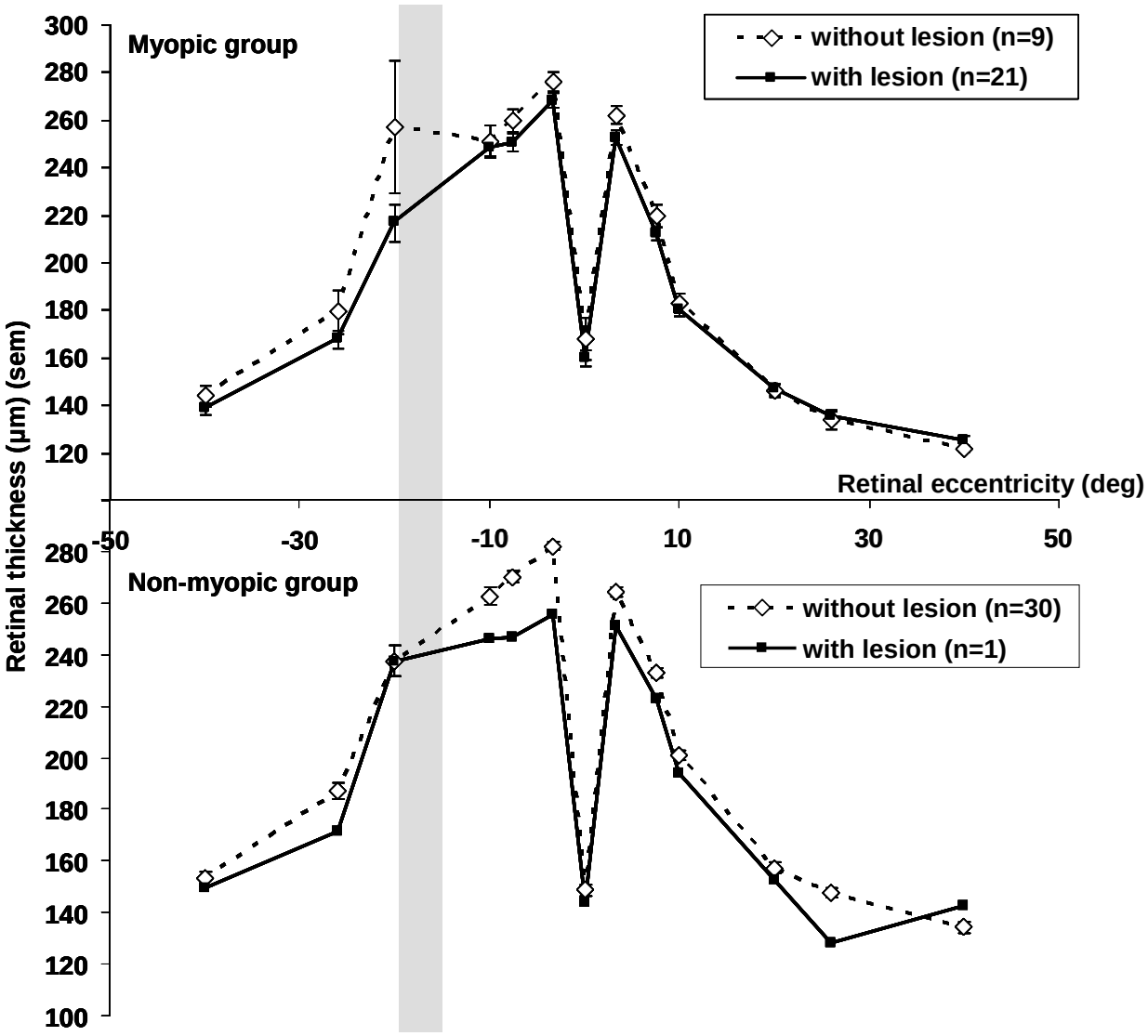


Figure 6.4-5 Retinal thickness profiles between eyes with and without retinal lesions among myopic and non-myopic groups

6.5. Discussion

OCT has been reported to yield repeatable and reproducible retinal thickness measurements in both macular and optic disc areas (Koozekanani *et al.*, 2000, Jones *et al.*, 2001, Massin *et al.*, 2001, Muscat *et al.*, 2002, Browning and Fraser, 2004, Paunescu *et al.*, 2004). Koozekanani *et al*. (2000) investigated the intersession repeatability of macular thickness measurements using OCT. Twenty six normal subjects ranged from 20 to 52 years were measured for their macular thickness using Humphrey 2000 OCT system. There were no significant changes between different visits ($P = 0.529$) or between different scans within the same visit ($P = 0.509$). They revealed the average macular thickness was found to be 274 ± 17 μm for a 1-mm long region 0.75 mm from the fovea. Muscat *et al.*(2002) measured 20 normal subjects (averaged age 31.9, ranged 21 - 57) for their macular thicknesses using Humphrey OCT system. They demonstrated that the coefficients of repeatability were between 1% to 2%, and they revealed that there was significant difference in macular thickness between men and women, the average macular thickness was 178 ± 18 μm in the women and 190 ± 24 μm in the men.

Browning and Fraser (2004) also studied the intraobserver variability of the OCT in patients with stable maculae and analyzed with ordinary least products analysis and Bland-Altman plots. They revealed that the foveal thickness and total macular volume measurements had low intraobserver variabilities, the coefficient of repeatability for foveal zone thickness was 37.0 μm and that for total macular volume was 0.29 mm^3.

Paunescu *et al*. (2004) investigated the measurement reproducibility of the third generation of commercial optical coherence tomography, Stratus OCT, software version A2 (Carl Zeiss Meditec, Dublin, CA). Ten normal subjects were imaged three times with natural pupils and three times with dilated pupils each day in random order, and the measurements were repeated on three different visits. Standard-density (128 A-scans per macular and optic nerve head (ONH) image and 256 A-scans per nerve fiber layer (NFL) image) and high-density (512 A-scans per image for all three scan types) scans were performed separately in each visit. They reported that the mean macular thickness was 235 ± 9.8 μm and the mean NFL thickness for standard scanning was 98 ± 9 μm. They showed that higher A-scan density (or image acquisition speed) significantly improved ($P < 0.05$) the reproducibility of the mean macular thickness, macular volume, and a

few sectors of the macular map, while there was no significant difference in macular measurements between natural and dilated pupil conditions. Standard-density scanning with dilated pupil demonstrated better reproducibility for most of the NFL parameters.

Fast Macular Thickness Map and Fast RNFL Thickness scans have been reported to have similar results compared with their conventional counterparts – Macular Thickness Map and RNFL Thickness scans, respectively. Zundane *et al*. (2005) followed fourteen diabetic patients with macular edema for three months with clinical eye examinations every two weeks. They performed both Macular Thickness map and Fast Macular Thickness Map using OCT 3 at each visit, and reported no significant difference between the two macular scanning protocols. Naheedy *et al*. (2004) compared the Macular Map and Fast Macular Map protocols of OCT 3 with twenty eyes from twenty normal subjects. They pointed out that there was no significant difference in macular volume as measured by Macular Map and Fast Macular Map.

To the best of our knowledge, this is the first report of the retinal thickness profile encompassing the central eighty degrees of the retina. With a modified

fixation target, we demonstrated good repeatability in the measurement of peripheral retinal thickness using the OCT. However, there are a few technical issues that require special attention. The range of eccentric retinal thickness measurements was limited by the field of fixation. Steady fixation must be achieved. At the extremities of the field of fixation, involuntary eye movements caused by fatigue often occur. Consequently, it is important to avoid extreme gaze. In addition, the fixation target must not be blocked by the OCT instrument. These limitations complicated the measurement along the vertical meridian. For these reasons, we used the horizontal meridian. However, this also has a limitation. Measurement along the horizontal meridian involved the region of the optic disk which is not ideal for comparison of retinal thickness nasal and temporal to the fovea.

Our study investigated the peripheral retina from 40 degrees nasal to 40 degrees temporal, and our data show that retinal thickness is significantly thinner in myopic eyes compared to non-myopic eyes (Table 6.4-2). Chujo *et al.* (1983) used ultrasonography to measure retinal thickness at the mid-posterior region in 5 eyes with high myopia (-8 to -12 D). They reported average retinal thickness of 116.2 ± 7.6 μm at the mid-posterior region. They commented that this was

thinner compared to 132 ± 6 μm in normal eyes. Wolsley *et al.* (2008) investigated the retinal thickness in myopic eyes from 16 degrees superior temporal to 16 degrees inferior nasal retina using the OCT. They found that peripheral retinal thickness decreased as myopia increased within a spherical equivalent range of 0.00 D to -15.00 D. There appears to be general agreement that the peripheral retinal thickness in myopic eyes is thinner compared to non-myopic eyes.

On the whole, the peripheral retinal thickness of myopic eyes was about 7% thinner than the retinal thickness of non-myopic eyes, independent of retinal location. This even thinning of the peripheral retina suggests that retinal stretching is relatively even across the retina in the myopic eye. This provides support to the suggestion of uniform retinal stretching at the region of central 30 degrees in the global expansion model of myopia progression (Chui *et al.*, 2005).

The retinal thickness was separated into two layers for analysis; the photoreceptor layer (from retinal pigment epithelium to outer nuclear layer) and the mid-inner layer (from outer plexiform layer to nerve fibre layer). Myopic eyes had a thinner photoreceptor layer at peripheral retinal locations compared to

non-myopic eyes. At the mid-inner layer, the picture is less clear cut. At the 10 degrees and 26 degrees temporal locations, the mid-inner layer was significantly thinner in myopic eyes compared to non-myopic eyes but this could not be demonstrated for other retinal locations. To an extent, our findings concur with the findings by Wolsley *et al.* (2008); their study which used retinal locations 16 degrees temporal and nasal retinal of the fovea, found that the photoreceptor layer thickness in myopic eyes and non-myopic eyes were the same. We had a similar finding. However, at more peripheral retinal locations, we found that this layer was thinner in myopic eyes. As for the mid-inner retinal layer thickness, Wolsley *et al.* (2008) reported that this layer was thinner in myopic eyes compared to non-myopic eyes. Our findings were less equivocal.

Why would the photoreceptor layer be thinner at more peripheral retinal locations? One reason might be that there is re-orientation of photoreceptors (Crewther, 2000) in a larger myopic eye. As the eyeball enlarges, the photoreceptors in the peripheral retina require significant re-orientation in order to be optimally aligned with the nodal point of the eye. This may cause the photoreceptor layer to become thinner. Another reason for a thinner photoreceptor layer in the myopic retina might be the "stretching" effect from an

elongated eye. As the eye elongates, a larger surface area of retina results in a lower photoreceptor density (Kitaguchi *et al.*, 2007) and this effect would be more significant in peripheral retinal locations than central retinal locations. Based on this argument and the fact that we did not find a thinner mid-inner retinal layer in myopic eyes, we suspect that the mid-inner retinal layer might not stretch but more tissues are laid down as the eye enlarges. For example, glial tissue. Lindqvist *et al.* (2010) found Muller cells sensed and responded fast to retinal stretching in the Guinea pig model. If the glial tissue growth takes place in the mid-inner retina, thinning of the retinal thickness might be the result of reduced photoreceptor density or its orientation. It is unknown that whether the glial tissue growth would be so even in order to achieve the uniform reduction in retinal thickness across eccentricity.

There are several limitations in the manual delineation of the photoreceptor layer and the mid-inner retinal layer, especially at peripheral retinal locations. At 40 degrees eccentricity, we found that it was difficult to determine the zone of separation between the photoreceptor retinal layer and mid-inner retinal layer due to the relatively low resolution of the OCT instrument. The tightly packed layers at peripheral retinal locations were difficult to resolve using the naked eye. In

addition, in the measurement of distance using the software calliper in the OCT, each pixel represented an 8-micron step. In terms of the thickness of the photoreceptor layer, the error introduced as a result of 1 pixel displacement was easily over 10% of the thickness of the layer measured. Wolsley *et al.*(2008) suggested that the thinning of retinal thickness with increasing myopia might be due to reduced thickness of the outer plexiform layer to the nerve fibre layer (mid-inner retinal layer). However, in our observations, the significant reduction of the mid-inner retinal layer was only found in the 10 and 26 degree temporal retina locations. Moreover, we observed a significant reduction in photoreceptor layer thickness in more eccentric retina, at 26 and 40 degree nasally and temporally.

There may be some lateral and axial distortion in the processing of OCT image as discussed by Podoleanu *et al.* (2004) but given that in our study only one acquisition point was used for each measurement of retinal thickness, and our OCT images were flat rather than bending upwards, any influence on the accuracy of OCT thickness measurement would be minimal.

The eccentric fixation device was mounted on the head rest of the OCT instrument, independent of the operation of the OCT scan head, with LED at 40 cm which subtends 40 degree (Figure 6.3-2). The pivotal point (PP) could be horizontally adjusted and was the designated point to coincide with the centre of eye rotation (CR), thus the visual axis of the subject's eye would be aligned correctly (Figure 6.3-2b). However, there was a possible error caused by relative positioning of CR with PP. Since there might be variation of the location of CR between subjects, Figure 6.3-2c, Figure 6.3-2d show the possible error in measuring angle due to CR not coinciding with PP. However, the error in the coincidence of the centre of eye rotation and the pivotal point would be caused by the relative position of the head rest of the OCT instrument and the apex of the eye, rather than the axial length variation.

CR could be either in front of or behind PP with a distance d, say ± 1 cm. The range of the centre of eye rotation was about 12–15 mm [c]. There would be an error in position from [-d -c] to [+d + c], that was [-1 -0.3] to [1 + 0.3], i.e. ±1.3 cm. This error would cause a variation in measuring angle from 38.8 to 41.2 degree. Since our findings showed that the retinal thickness reduction in myopic eyes was fairly constant, we believe the effect of this possible error was minimal.

The *in vivo* retinal thickness profiles in both refractive groups concur with current understanding of retina anatomy (Snell and Lemp, 1998) that the thinnest part in retina is the foveola, while the thickest part is at the parafoveal region (i.e. the 4 quadrants in the inner ring). The retinal thickness reduces towards the periphery except at the optic disc area (about 20-degree nasal retina).

We used the Macular Thickness Map pattern provided by the StratusOCT. The retinal thicknesses we measured in all zones were similar to other studies which used the same pattern (Luo *et al.*, 2006, Lam *et al.*, 2007). Luo *et al.* (2006) reported that higher myopia was associated with reduced macular thickness and volume in all zones except the fovea. They also found that higher myopia was associated with greater foveal thickness. However, they did not find any significant correlation between averaged macular thickness and SER or axial length. Lam *et al.* (2007) reported regional variations in the association between macular thickness and myopia. The averaged foveal thicknesses were significantly greater in higher myopia, while the outer ring macula thickness locations were significantly thinner with higher myopia. Lam *et al.* (2007) found insignificant relationship in the inner ring macular thickness and refractive error.

They found axial length was positively correlated with averaged foveal thickness and negatively correlated with outer macular thickness and averaged macular thickness.

In common with other studies (Luo *et al.*, 2006, Lam *et al.*, 2007), we found that the non-myopic group had significantly thicker retinas than the myopic group. However, at foveal region, the myopic group showed a thicker retina than the non-myopic group. This has been reported previously (Luo *et al.*, 2006, Lam *et al.*, 2007). The underlying reason for the foveal thickening remains unclear. Our results show that myopic eyes and non-myopic eyes were not different in photoreceptor layer thickness at the fovea. Our mean photoreceptor layer thickness for myopic and non-myopic eyes was similar to the normative data of photoreceptor layer thickness reported by Christensen *et al.* (2008). However, myopic eyes had significantly thicker mid-inner retinal layer than non-myopic eyes at the fovea. It has also been observed in a study (Dubis *et al.*, 2009) that the foveal pit is more shallow in myopic eyes. Interestingly, Panozzo and Mercanti (2004) reported that epiretinal traction is a common sign in degenerative myopia where the foveal thickness might be more than 200 μm. Perhaps epiretinal

traction might be one of the factors causing the mid-inner retinal layer to be thicker in myopic eyes.

Axial elongation in myopia increases the chance of retinal peripheral degenerations (Celorio and Pruett, 1991, Pierro *et al.*, 1992, Lam *et al.*, 2005, Saw *et al.*, 2005b). We wondered whether this was associated with the retinal thinning found in myopic eyes. In our sample, the frequency of peripheral retinal degeneration was higher in the myopic group compared to the non-myopic group. However, on further analysis, we found that there was no difference in retinal thickness between subjects with and without peripheral retinal degenerations within the myopia and non-myopic groups. This informs us that retinal thickness is not a good predictor for the occurrence of peripheral retinal lesions and suggests that there may be more complicated factors at play in the genesis of peripheral retinal lesions associated with myopia. Perhaps further analysis on the localized retinal thickness variation is needed for whether retinal lesions play a role in retinal thickness.

A weakness of our study was that the OCT instrument we used was an older model. Later models have higher resolution and may enable the various layers of

the retina to be distinguished relatively easier. Future studies on changes in the specific retinal layers will benefit from using higher resolution OCT.

6.6. Conclusions

This study established the retinal thickness profiles in the central horizontal eighty degrees in myopic and non-myopic eyes. Myopic eyes have a thicker retina at the fovea and thinner retina at other regions compared to non-myopic eyes. From 40-degree nasal to 40-degree temporal retina, the peripheral retinal thickness was approximately 7% less in myopic eyes compared to the non-myopic eyes. Although myopic eyes were more likely to have peripheral lesions, retinal thickness was not an important factor associated with these lesions.

7. Chapter Seven. Overall summary and concluding remarks

It has been reported that sight threatening retinal complications are associated with high myopia more than -6 D in the adult population. High myopia a leading cause of blindness, contributed around 6% to 13% of blindness as reported in previous worldwide studies. Myopia, especially high myopia and its prevalence, etiology, associated complications and current knowledge gaps was discussed in Chapters 1 to 3.

In cities like Hong Kong where the prevalence of myopia is in the range of 70% to 80%; myopia starts as early as the start of schooling and progresses steadily throughout the schooling period. The prevalence of high myopia presents a threat to the visual quality of this population. To date, there was little information on the early changes in the retina, as well as the consequence of high myopia among schoolchildren and adolescents that would lead to retinal complications or other ocular pathologies.

In identifying an efficient and effective method to detect the early retinal changes among the adolescent group, the latest available technology and instrumentation

were explored in Chapter 4. The Optomap was selected for the investigation because of its sensitivity and specificity in fundus screening.

In Chapter 4, our study investigated the effectiveness of retinal screening with the Optomap ultra wide field scanning laser ophthalmoscope and found that sensitivity and specificity was averaged 76.4% and 71.9%, respectively, as compared with standard dilated fundus examination with binocular indirect ophthalmoscopy. The use of cotton bud lid retraction reduced imperfections during image capture. The Optomap permits fundus examination without the use of a mydriatic agent, which is more comfortable for the patients, and a permanent digital record of the findings can be kept. When the benefits of Optomap and the costs of preventing vision-threatening peripheral retinal diseases are considered, the instrument certainly provides an alternative for patients in whom a routine dilated examination is not indicated.

However, there are still some shortfalls including the possibility that retinal lesions at the outside edges of the retina might not be identified and the fact that the colours of the Optomap are the artificial combination of two laser channels, resulting in a distorted image. The Optomap is a complementary method to the

standard dilated fundus examination but not a substitute, especially in a high risk group of having retinal lesions such as the high myopic population.

The major concern in this whole study was to determine the prevalence of myopic related to early changes in the retina among school children and adolescents having high myopia and whether these retinal changes are any different from those of the adult population. This information may help to identify the possible risk factors including biometric and demographic characteristics for children or adolescents having high myopia ocular complications in their later years.

In Chapter 5, the myopia related retinal changes in high myopic adolescence were investigated. Peripheral retinal degenerative lesions and optic nerve crescent were found in a significant proportion of high myopic teenage subjects. Myopic related fundus changes could appear in early life in high myopic eyes. The five most frequent retinal lesions found in the eyes were; optic nerve crescents (52.5%), white-without-pressure (51.7%), lattice degeneration (5.8%), microcystoid degeneration (5%) and pigmentary degeneration (4.2%). This leads to concerns of retinal examination in young high myopes since predisposing

factor of retinal detachment like lattice degeneration could manifest at early as 12 years old, and it was one of the most frequent retinal lesions found in our study. Detailed analysis with Chi-square and multiple logistic regressions was performed to investigate a number of factors including; pathological myopia, axial length, age, gender, familial retinal history, number of years of having myopia, and IOP. The results showed that axial length longer than 26.5 mm was the significant risk factor for peripheral lesions ($p = 0.008$, odd ratio 3.37), optic nerve crescents ($p = 0.019$, odd ratio 2.80) and white-without-pressure ($p = 0.017$, odd ratio 2.93). Our results showed that the prevalence of lattice degeneration among 12 - 18 year-old high myopia schoolchildren was lower than the prevalence in an adult high myopic population as previously reported. There was a positive relationship between axial length and peripheral retinal lesions. There is a higher chance of having retinal lesions in eyes with axial lengths exceeding 26.5 mm between 12 - 18 years of age.

While myopia related retinal changes are present among this age group, there are no urgent sight-threatening types of retinal lesion reported in our study. However, lesion like lattice degeneration is a predisposing factor of retinal detachment. Thus an early detection and assessment of fundal changes among young high

myopes is important.

To further understand how the retina changes in a bigger eye, as a result of myopia progression and axial elongation, the retinal thickness variation along the horizontal meridian were also investigated in Chapter 6. This may lead to an understanding of the relationship between the anatomical variations and retinal complications.

Chapter 6 established the retinal thickness profiles in the central horizontal eighty degrees in myopic and non-myopic eyes. Myopic eyes have a thicker retina at the foveal center and fovea ($p = 0.002$ and 0.044 respectively), and thinner retina at other regions compared to non-myopic eyes ($p < 0.01$, unpaired t-test). At non-foveal zones of the macula, the retina was significantly thinner in myopic eyes compared to non-myopic eyes ($p < 0.01$, unpaired t-test). From 40 degree nasal to 40 degree temporal retina, a general reduction of retinal thickness was observed across the myopic retina compared to the non-myopic retina, except at 20 degrees nasal to fixation. The peripheral retinal thickness was approximately 7% thinner in myopic eyes compared to the non-myopic eyes. Although myopic eyes were more likely to have peripheral lesions, there is no

evidence that relates retinal thickness as an important factor associated with these lesions.

Retinal thickness reduction is associated with high myopia as found in our study. There is a lot more to be done, such as correlating retinal changes with visual changes, and longitudinal monitoring to observe the changes over time.

In conclusion, high myopia may lead to ocular complications especially at the retina, even in younger age. Axial length measurement is encouraged for high myopic subjects since it might be a predictor for peripheral retinal lesions. The thinning of the retina in high myopic eyes is a general reduction in thickness, at least within the central 80 degrees. There should be a more structured investigation of this topic and aimed at looking for effective and efficient means to identify subjects having ocular problems with high myopia and provide timely and appropriate treatment.

Reference

Anderson, D. C., Lucas, R. A. and Henderson, R. (1998). Wide field scanning laser ophthalmoscope, OPTOS Public Limited Company, United States.

Atchison, D. A., Jones, C. E., Schmid, K. L., *et al.* (2004). Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci* **45**, 3380-3386.

Atchison, D. A., Pritchard, N., Schmid, K. L., Scott, D. H., Jones, C. E. and Pope, J. M. (2005). Shape of the retinal surface in emmetropia and myopia. *Invest Ophthalmol Vis Sci* **46**, 2698-2707.

Attebo, K., Ivers, R. Q. and Mitchell, P. (1999). Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology* **106**, 1066-1072.

Avisar, R., Friling, R., Snir, M., Avisar, I. and Weinberger, D. (2006). Estimation of prevalence and incidence rates and causes of blindness in Israel, 1998-2003. *Isr Med Assoc J* **8**, 880-881.

Ayed, T., Sokkah, M., Charfi, O. and El Matri, L. (2002). [Epidemiologic study of refractive errors in schoolchildren in socioeconomically deprived regions in Tunisia]. *J Fr Ophtalmol* **25**, 712-717.

Bansal, A. S. and Hubbard, G. B., 3rd (2010). Peripheral retinal findings in highly myopic children < or =10 years of age. *Retina* **30**, S15-19.

Batchelder, T. J., Fireman, B., Friedman, G. D., *et al.* (1997). The value of routine dilated pupil screening examination. *Arch Ophthalmol* **115**, 1179-1184.

Bec, P., Ravault, M., Arne, J.-L. and Trepsat, C. (1985a). *The Fundus periphery : report of the French Society of Ophthalmology*. Masson Pub. USA, New York.

Bec, P., Ravault, M., Arne, J.-L. and Trepsat, C. (1985b). The fundus periphery in myopia. In: *The fundus periphery : report of the French Society of Ophthalmology*, Masson Pub. USA, New York, pp 394-399.

Berendschot, T. T., Delint, P. J. and Van Norren, D. (2003). Fundus reflectance--historical and present ideas. *Prog Retin Eye Res* **22**, 171-200.

Berntsen, D. A., Mutti, D. O. and Zadnik, K. (2010). The effect of bifocal add on accommodative lag in myopic children with high accommodative lag. *Invest Ophthalmol Vis Sci* **51**, 6104-6110.

Bland, J. M. and Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1**, 307-310.

Bradley, A., Rabin, J. and Freeman, R. D. (1983). Nonoptical determinants of aniseikonia. *Invest Ophthalmol Vis Sci* **24**, 507-512.

Browning, D. J. and Fraser, C. M. (2004). Intraobserver variability in optical coherence tomography. *Am J Ophthalmol* **138**, 477-479.

Byer, N. E. (1979). Lattice degeneration of the retina. *Surv Ophthalmol* **23**, 213-248.

Carney, L. G., Mainstone, J. C. and Henderson, B. A. (1997). Corneal topography and myopia. A cross-sectional study. *Invest Ophthalmol Vis Sci* **38**, 311-320.

Cedrone, C., Nucci, C., Scuderi, G., Ricci, F., Cerulli, A. and Culasso, F. (2006). Prevalence of blindness and low vision in an Italian population: a comparison with other European studies. *Eye (Lond)* **20**, 661-667.

Celorio, J. M. and Pruett, R. C. (1991). Prevalence of lattice degeneration and its relation to axial length in severe myopia. *Am J Ophthalmol* **111**, 20-23.

Chan, O. Y. and Edwards, M. (1993). Refractive errors in Hong Kong Chinese pre-school children. *Optom Vis Sci* **70**, 501-505.

Chang, P. Y., Yang, C. M., Yang, C. H., *et al.* (2005). Clinical characteristics and surgical outcomes of pediatric rhegmatogenous retinal detachment in Taiwan. *Am J Ophthalmol* **139**, 1067-1072.

Cho, P., Cheung, S. W. and Edwards, M. (2005). The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. *Curr Eye Res* **30**, 71-80.

Christensen, U., Kroyer, K., Thomadsen, J., Jorgensen, T., Cour, M. L. and Sander, B. (2008). Normative data of outer photoreceptor layer thickness obtained by software image enhancing based on Stratus optical coherence tomography images. *Br J Ophthalmol* **92**, 800-805.

Chui, T. Y., Yap, M. K., Chan, H. H. and Thibos, L. N. (2005). Retinal stretching limits peripheral visual acuity in myopia. *Vision Res* **45**, 593-605.

Chujo, S., Kobayashi, Y., Emi, K., Fujioka, C. and Yokoyama, M. (1983). [The biometry of each thickness of the human retina, choroid and sclera by using ultrasound and Fourier analysis. High myopia]. *Nippon Ganka Gakkai Zasshi* **87**, 70-73.

Collins, J. W. and Carney, L. G. (1990). Visual performance in high myopia. *Current eye research* **9**, 217-223.

Crewther, D. P. (2000). The role of photoreceptors in the control of refractive state. *Prog Retin Eye Res* **19**, 421-457.

Curtin, B. J. (1985). *The myopias : basic science and clinical management*. Harper & Row, Philadelphia.

Curtin, B. J. and Karlin, D. B. (1971). Axial length measurements and fundus changes of the myopic eye. *American journal of ophthalmology* **1**, 42-53.

Czepita, D., Goslawski, W. and Mojsa, A. (2003). [Occurrence of myopia among Polish students aged 6 to 18 years old]. *Klin Oczna* **105**, 52-56.

Dandona, R., Dandona, L., Srinivas, M., Giridhar, P., Mccarty, C. A. and Rao, G. N. (2002). Population-based assessment of refractive error in India: the Andhra Pradesh eye disease study. *Clin Experiment Ophthalmol* **30**, 84-93.

Daniel, W. W. (1999). *Biostatistics : a foundation for analysis in the health sciences*. Wiley, New York.

Daubs, J. G. and Crick, R. P. (1981). Effect of refractive error on the risk of ocular hypertension and open angle glaucoma. *Trans Ophthalmol Soc U K* **101**, 121-126.

Dirani, M., Tong, L., Gazzard, G., *et al.* (2009). Outdoor activity and myopia in Singapore teenage children. *Br J Ophthalmol* **93**, 997-1000.

Dubis, A., Mcallister, J. T. and Carroll, J. (2009). Reconstructing foveal pit morphology from optical coherence tomography imaging. *Br J Ophthalmol*, bjo.2008.150110 (Epub ahead of print).

Duke-Elder, S. (1970). Pathological refractive errors. In: *System of Ophthalmology* (ed S. Duke-Elder), Mosby, St. Louis, pp 297-373.

Edwards, M. and Yap, M. (1990). Visual problems in Hong Kong primary school children. *Clin Exp Optom* **73**, 58-63.

Edwards, M. H. (1999). The development of myopia in Hong Kong children between the ages of 7 and 12 years: a five-year longitudinal study. *Ophthalmic Physiol Opt* **19**, 286-294.

Escalona-Benz, E., Murray, T. G., Benz, M. S., Villate, N. and Hayden, B. C. (2003). Correlation between Optos Ultra Widefield Digital Imaging, Standardized Fundus Photography, and B-Scan Echography in the Detection of Posterior Segment Tumors. *Invest. Ophthalmol. Vis. Sci.* **44**, 3644-.

Fan, D. S., Lam, D. S., Lam, R. F., *et al.* (2004). Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci* **45**, 1071-1075.

Fan, D. S., Lam, D. S. and Li, K. K. (1999). Retinal complications after cataract extraction in patients with high myopia. *Ophthalmology* **106**, 688-691; discussion 691-682.

Fan, D. S. P., Lai, C., Lau, H. H. W., Cheung, E. Y. Y. and Lam, D. S. C. (2011). Change in vision disorders among Hong Kong preschoolers in 10 years. *Clinical & Experimental Ophthalmology* **39**, 398-403.

Fedtke, C., Ehrmann, K. and Holden, B. A. (2009). A review of peripheral refraction techniques. *Optom Vis Sci* **86**, 429-446.

Fledelius, H. C. (2000). Myopia profile in Copenhagen medical students 1996-98. Refractive stability over a century is suggested. *Acta Ophthalmol Scand* **78**, 501-505.

Friberg, T. R. (1994). Examination of the Retina: Ophthalmoscopy and Fundus Biomicroscopy. In: *Principles and practice of ophthalmology : clinical practice* (eds D. M. Albert and F. A. Jakobiec), Saunders, Philadelphia, pp 686-697.

Friberg, T. R., Pandya, A. and Eller, A. W. (2003). Non-mydriatic panoramic fundus imaging using a non-contact scanning laser-based system. *Ophthalmic Surg Lasers Imaging* **34**, 488-497.

Ghafour, I. M., Allan, D. and Foulds, W. S. (1983). Common causes of blindness and visual handicap in the west of Scotland. *Br J Ophthalmol* **67**, 209-213.

Go, S. L., Hoyng, C. B. and Klaver, C. C. (2005). Genetic risk of rhegmatogenous retinal detachment: a familial aggregation study. *Arch Ophthalmol* **123**, 1237-1241.

Goh, W. S. and Lam, C. S. (1994). Changes in refractive trends and optical components of Hong Kong Chinese aged 19-39 years. *Ophthalmic Physiol Opt* **14**, 378-382.

Goldschmidt, E. (1998). Epidemiology of myopia: Scandinavian and Hong Kong Experiences. In: *Myopia updates: Proceedings of the 6th International Conference on Myopia* (ed T. Tokoro), Springer, pp 3-12.

Goss, D. A. (1987). Linearity of refractive change with age in childhood myopia progression. *Am J Optom Physiol Opt* **64**, 775-780.

Goss, D. A., Hampton, M. J. and Wickham, M. G. (1988). Selected review on genetic factors in myopia. *J Am Optom Assoc* **59**, 875-884.

Goss, D. A. and Wickham, M. G. (1995). Retinal-image mediated ocular growth as a mechanism for juvenile onset myopia and for emmetropization. A literature review. *Doc Ophthalmol* **90**, 341-375.

Gozum, N., Cakir, M., Gucukoglu, A. and Sezen, F. (1997). Relationship between retinal lesions and axial length, age and sex in high myopia. *Eur J Ophthalmol* **7**, 277-282.

Grodum, K., Heijl, A. and Bengtsson, B. (2001). Refractive error and glaucoma. *Acta Ophthalmol Scand* **79**, 560-566.

Grosvenor, T. (1987). A review and a suggested classification system for myopia on the basis of age-related prevalence and age of onset. *Am J Optom Physiol Opt* **64**, 545-554.

Grosvenor, T. (2003). Why is there an epidemic of myopia? *Clin Exp Optom* **86**, 273-275.

Grosvenor, T. P. and Goss, D. A. (1999). *Clinical management of myopia*. Butterworth-Heinemann, Boston.

Guggenheim, J. A., Kirov, G. and Hodson, S. A. (2000). The heritability of high myopia: a reanalysis of Goldschmidt's data. *Journal of medical genetics* **37**, 227-231.

Gwiazda, J., Hyman, L., Dong, L. M., *et al.* (2007). Factors associated with high myopia after 7 years of follow-up in the Correction of Myopia Evaluation Trial (COMET) Cohort. *Ophthalmic epidemiology* **14**, 230-237.

Gwiazda, J., Hyman, L., Hussein, M., *et al.* (2003). A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci* **44**, 1492-1500.

Hammond, C. J., Snieder, H., Gilbert, C. E. and Spector, T. D. (2001). Genes and environment in refractive error: the twin eye study. *Invest Ophthalmol Vis Sci* **42**, 1232-1236.

Han, W., Leung, K. H., Fung, W. Y., *et al.* (2009). Association of PAX6 polymorphisms with high myopia in Han Chinese nuclear families. *Invest Ophthalmol Vis Sci* **50**, 47-56.

Han, W., Yap, M. K., Wang, J. and Yip, S. P. (2006). Family-based association analysis of hepatocyte growth factor (HGF) gene polymorphisms in high myopia. *Invest Ophthalmol Vis Sci* **47**, 2291-2299.

Heath, S., Robledo, R., Beggs, W., *et al.* (2001). A novel approach to search for identity by descent in small samples of patients and controls from the same mendelian breeding unit: a pilot study on myopia. *Hum Hered* **52**, 183-190.

Hee, M. R., Izatt, J. A., Swanson, E. A., *et al.* (1995). Optical coherence tomography of the human retina. *Arch Ophthalmol* **113**, 325-332.

Ho, T., Shih, Y., Lin, L., Liu, K., Yang, C. and Chiang, L. (1994). Prevalence of retinal detachment and peripheral retinal degenerations in high myopic

college students in Taiwan. In: *Proc 5th Intl Conf Myopia, MIRF*, pp 160-161.

Hornbeak, D. M. and Young, T. L. (2009). Myopia genetics: a review of current research and emerging trends. *Curr Opin Ophthalmol* **20**, 356-362.

Huang, D., Swanson, E. A., Lin, C. P., *et al.* (1991). Optical coherence tomography. *Science* **254**, 1178-1181.

Huang, S. J. (1993). [Early change of visual function in high myopia--measured and analyzed by octopus automated perimeter]. *Nippon Ganka Gakkai Zasshi* **97**, 881-887.

Hyams, S. W. and Neumann, E. (1969). Peripheral retina in myopia. With particular reference to retinal breaks. *Br J Ophthalmol* **53**, 300-306.

Hyman, L., Gwiazda, J., Hussein, M., *et al.* (2005). Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol* **123**, 977-987.

Ip, J. M., Huynh, S. C., Robaei, D., *et al.* (2008a). Ethnic differences in refraction and ocular biometry in a population-based sample of 11-15-year-old Australian children. *Eye (London, England)* **22**, 649-656.

Ip, J. M., Rose, K. A., Morgan, I. G., Burlutsky, G. and Mitchell, P. (2008b). Myopia and the urban environment: findings in a sample of 12-year-old Australian school children. *Investigative ophthalmology & visual science* **49**, 3858-3863.

Ip, J. M., Saw, S. M., Rose, K. A., *et al.* (2008c). Role of near work in myopia: findings in a sample of Australian school children. *Investigative ophthalmology & visual science* **49**, 2903-2910.

Ivers, R. Q., Mitchell, P. and Cumming, R. G. (1999). Sensory impairment and driving: the Blue Mountains Eye Study. *Am J Public Health* **89**, 85-87.

Jones, A. L., Sheen, N. J., North, R. V. and Morgan, J. E. (2001). The Humphrey optical coherence tomography scanner: quantitative analysis and reproducibility study of the normal human retinal nerve fibre layer. *Br J Ophthalmol* **85**, 673-677.

Jorge, J., Almeida, J. B. and Parafita, M. A. (2007). Refractive, biometric and topographic changes among Portuguese university science students: a 3-year longitudinal study. *Ophthalmic Physiol Opt* **27**, 287-294.

Junghans, B., Kiely, P. M., Crewther, D. P. and Crewther, S. G. (2002). Referral rates for a functional vision screening among a large cosmopolitan sample of Australian children. *Ophthalmic Physiol Opt* **22**, 10-25.

Junghans, B. M. and Crewther, S. G. (2005). Little evidence for an epidemic of myopia in Australian primary school children over the last 30 years. *BMC Ophthalmol* **5**, 1.

Karlin, D. B. and Curtin, B. J. (1976). Peripheral chorioretinal lesions and axial length of the myopic eye. *American journal of ophthalmology* **81**, 625-635.

Kirker, G. E. and Mcdonald, D. J. (1971). Peripheral retinal degeneration in high myopia. *Can J Ophthalmol* **6**, 58-61.

Kitaguchi, Y., Bessho, K., Yamaguchi, T., Nakazawa, N., Mihashi, T. and Fujikado, T. (2007). In vivo measurements of cone photoreceptor spacing in myopic eyes from images obtained by an adaptive optics fundus camera. *Jpn J Ophthalmol* **51**, 456-461.

Kleinstein, R. N., Jones, L. A., Hullett, S., *et al.* (2003). Refractive error and ethnicity in children. *Arch Ophthalmol* **121**, 1141-1147.

Kobayashi, K., Ohno-Matsui, K., Kojima, A., *et al.* (2005). Fundus characteristics of high myopia in children. *Jpn J Ophthalmol* **49**, 306-311.

Koozekanani, D., Roberts, C., Katz, S. E. and Herderick, E. E. (2000). Intersession repeatability of macular thickness measurements with the Humphrey 2000 OCT. *Invest Ophthalmol Vis Sci* **41**, 1486-1491.

Ku, W. C., Chuang, L. H. and Lai, C. C. (2002). Cataract extraction in high myopic eyes. *Chang Gung medical journal* **25**, 315-320.

Lai, T. Y., Fan, D. S., Lai, W. W. and Lam, D. S. (2008). Peripheral and posterior pole retinal lesions in association with high myopia: a cross-sectional community-based study in Hong Kong. *Eye (Lond)* **22**, 209-213.

Lam, C. and Goh, W. (1991). The incidence of refractive errors among schoolchildren in Hong Kong and its relationship with the optical components. *Clin Exp Optom* **74**, 97-103.

Lam, C. S., Edwards, M., Millodot, M. and Goh, W. S. (1999). A 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. *Optom Vis Sci* **76**, 370-380.

Lam, C. S., Goh, W. S., Tang, Y. K., Tsui, K. K., Wong, W. C. and Man, T. C. (1994). Changes in refractive trends and optical components of Hong Kong Chinese aged over 40 years. *Ophthalmic Physiol Opt* **14**, 383-388.

Lam, C. S., Lam, C. H., Cheng, S. C. and Chan, L. Y. (2012). Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *Ophthalmic Physiol Opt* **32**, 17-24.

Lam, D. S., Fan, D. S., Chan, W. M., *et al.* (2005). Prevalence and characteristics of peripheral retinal degeneration in Chinese adults with high myopia: a cross-sectional prevalence survey. *Optom Vis Sci* **82**, 235-238.

Lam, D. S., Leung, K. S., Mohamed, S., *et al.* (2007). Regional variations in the relationship between macular thickness measurements and myopia. *Invest Ophthalmol Vis Sci* **48**, 376-382.

Lee, K. E., Klein, B. E., Klein, R. and Wong, T. Y. (2002). Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. *Invest Ophthalmol Vis Sci* **43**, 2566-2571.

Lewis, H. (2003). Peripheral retinal degenerations and the risk of retinal detachment. *Am J Ophthalmol* **136**, 155-160.

Lim, M. C., Hoh, S. T., Foster, P. J., *et al.* (2005). Use of optical coherence tomography to assess variations in macular retinal thickness in myopia. *Invest Ophthalmol Vis Sci* **46**, 974-978.

Lim, R., Mitchell, P. and Cumming, R. G. (1999). Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* **40**, 3021-3026.

Lin, L. L., Shih, Y. F., Hsiao, C. K. and Chen, C. J. (2004). Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore* **33**, 27-33.

Lin, L. L., Shih, Y. F., Hsiao, C. K., Chen, C. J., Lee, L. A. and Hung, P. T. (2001). Epidemiologic study of the prevalence and severity of myopia among schoolchildren in Taiwan in 2000. *J Formos Med Assoc* **100**, 684-691.

Lindqvist, N., Liu, Q., Zajadacz, J., Franze, K. and Reichenbach, A. (2010). Retinal glial (Muller) cells: sensing and responding to tissue stretch. *Invest Ophthalmol Vis Sci* **51**, 1683-1690.

Lithander, J. (1999). Prevalence of myopia in school children in the Sultanate of Oman: a nation-wide study of 6292 randomly selected children. *Acta Ophthalmol Scand* **77**, 306-309.

Liu, H. H., Xu, L., Wang, Y. X., Wang, S., You, Q. S. and Jonas, J. B. (2010). Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. *Ophthalmology* **117**, 1763-1768.

Lo, P. I., Ho, P. C., Lau, J. T., Cheung, A. Y., Goldschmidt, E. and Tso, M. O. (1996). Relationship between myopia and optical components--a study among Chinese Hong Kong student population. *Yan Ke Xue Bao* **12**, 121-125.

Logan, N. S., Gilmartin, B., Marr, J. E., Stevenson, M. R. and Ainsworth, J. R. (2004). Community-based study of the association of high myopia in children with ocular and systemic disease. *Optom Vis Sci* **81**, 11-13.

Low, W., Dirani, M., Gazzard, G., *et al.* (2010). Family history, near work, outdoor activity, and myopia in Singapore Chinese preschool children. *Br J Ophthalmol* **94**, 1012-1016.

Luo, H. D., Gazzard, G., Fong, A., *et al.* (2006). Myopia, axial length, and OCT characteristics of the macula in Singaporean children. *Invest Ophthalmol Vis Sci* **47**, 2773-2781.

Lyhne, N., Sjolie, A. K., Kyvik, K. O. and Green, A. (2001). The importance of genes and environment for ocular refraction and its determiners: a population based study among 20-45 year old twins. *Br J Ophthalmol* **85**, 1470-1476.

Mackenzie, P. J., Russell, M., Ma, P. E., Isbister, C. M. and Maberley, D. A. (2007). Sensitivity and specificity of the optos optomap for detecting peripheral retinal lesions. *Retina* **27**, 1119-1124.

Massin, P., Vicaut, E., Haouchine, B., Erginay, A., Paques, M. and Gaudric, A. (2001). Reproducibility of retinal mapping using optical coherence tomography. *Arch Ophthalmol* **119**, 1135-1142.

Maul, E., Barroso, S., Munoz, S. R., Sperduto, R. D. and Ellwein, L. B. (2000). Refractive Error Study in Children: results from La Florida, Chile. *Am J Ophthalmol* **129**, 445-454.

Mavracanas, T. A., Mandalos, A., Peios, D., *et al.* (2000). Prevalence of myopia in a sample of Greek students. *Acta Ophthalmol Scand* **78**, 656-659.

Mcbrien, N. A. and Adams, D. W. (1997). A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. *Invest Ophthalmol Vis Sci* **38**, 321-333.

Mccarty, C. A., Mukesh, B. N., Fu, C. L. and Taylor, H. R. (1999). The epidemiology of cataract in Australia. *Am J Ophthalmol* **128**, 446-465.

Midelfart, A., Kinge, B., Midelfart, S. and Lydersen, S. (2002). Prevalence of refractive errors in young and middle-aged adults in Norway. *Acta Ophthalmol Scand* **80**, 501-505.

Mitchell, P., Hourihan, F., Sandbach, J. and Wang, J. J. (1999). The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology* **106**, 2010-2015.

Mitry, D., Williams, L., Charteris, D. G., Fleck, B. W., Wright, A. F. and Campbell, H. (2011). Population-based estimate of the sibling recurrence

risk ratio for rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci* **52**, 2551-2555.

Montes-Mico, R. and Ferrer-Blasco, T. (2000). Distribution of refractive errors in Spain. *Doc Ophthalmol* **101**, 25-33.

Morgan, I. and Rose, K. (2005). How genetic is school myopia? *Prog Retin Eye Res* **24**, 1-38.

Morgan, I. G. (2003). The biological basis of myopic refractive error. *Clin Exp Optom* **86**, 276-288.

Morgan, I. G., Rose, K. A., Smith, W. and Mitchell, P. (2004). Re: Evidence for an "epidemic" of myopia. *Ann Acad Med Singapore* **33**, 541-543; author reply 543; discussion 544.

Murthy, G. V., Gupta, S. K., Ellwein, L. B., *et al.* (2002). Refractive error in children in an urban population in New Delhi. *Invest Ophthalmol Vis Sci* **43**, 623-631.

Muscat, S., Parks, S., Kemp, E. and Keating, D. (2002). Repeatability and reproducibility of macular thickness measurements with the Humphrey OCT system. *Invest Ophthalmol Vis Sci* **43**, 490-495.

Mutti, D. O., Hayes, J. R., Mitchell, G. L., *et al.* (2007). Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci* **48**, 2510-2519.

Mutti, D. O., Mitchell, G. L., Moeschberger, M. L., Jones, L. A. and Zadnik, K. (2002). Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci* **43**, 3633-3640.

Mutti, D. O., Sholtz, R. I., Friedman, N. E. and Zadnik, K. (2000). Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci* **41**, 1022-1030.

Mutti, D. O. and Zadnik, K. (1995). The utility of three predictors of childhood myopia: a Bayesian analysis. *Vision research* **35**, 1345-1352.

Mutti, D. O., Zadnik, K. and Adams, A. J. (1996). Myopia. The nature versus nurture debate goes on. *Invest Ophthalmol Vis Sci* **37**, 952-957.

Naheedy, J. H., Bartsch, D.-U. and Freeman, W. R. (2004). Comparison of retinal thickness and macular volume using three imaging techniques. *Invest. Ophthalmol. Vis. Sci.* **45**, 2407-.

Naidoo, K. S., Raghunandan, A., Mashige, K. P., *et al.* (2003). Refractive error and visual impairment in African children in South Africa. *Invest Ophthalmol Vis Sci* **44**, 3764-3770.

Naiglin, L., Gazagne, C., Dallongeville, F., *et al.* (2002). A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. *J Med Genet* **39**, 118-124.

Nakazawa, M., Kurotaki, J. and Ruike, H. (2008). Longterm findings in peripapillary crescent formation in eyes with mild or moderate myopia. *Acta Ophthalmol* **86**, 626-629.

Nath, S., Sherman, J. and Battaglia, M. (2005). Is OPTOS Imaging Additive or Duplicative to a Dilated Fundus Exam? *Invest. Ophthalmol. Vis. Sci.* **46**, 1554-.

Nepal, B. P., Koirala, S., Adhikary, S. and Sharma, A. K. (2003). Ocular morbidity in schoolchildren in Kathmandu. *Br J Ophthalmol* **87**, 531-534.

O'brien, D. A. and Phillips, A. J. (2000). Stickler syndrome. *Clin Exp Optom* **83**, 330-332.

Optos (2001). *Panoramic200 User Guide*. Optos plc, Scotland.

Owens, H., Garner, L. F., Yap, M. K., Frith, M. J. and Kinnear, R. F. (1998). Age dependence of ocular biometric measurements under cycloplegia with tropicamide and cyclopentolate. *Clin Exp Optom* **81**, 159-162.

Pacella, R., Mclellan, J., Grice, K., Del Bono, E. A., Wiggs, J. L. and Gwiazda, J. E. (1999). Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. *Optom Vis Sci* **76**, 381-386.

Paluru, P., Ronan, S. M., Heon, E., *et al.* (2003). New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. *Invest Ophthalmol Vis Sci* **44**, 1830-1836.

Paluru, P. C., Nallasamy, S., Devoto, M., Rappaport, E. F. and Young, T. L. (2005). Identification of a novel locus on 2q for autosomal dominant high-grade myopia. *Invest Ophthalmol Vis Sci* **46**, 2300-2307.

Pandya, A., Friberg, T. and Eller, A. (2002). Optos Non-Mydriatic Widefield Imaging vs. Clinical Dilated Fundus Exam for Retinal Diagnosis and Management. *Invest. Ophthalmol. Vis. Sci.* **43**, 2860-.

Panozzo, G. and Mercanti, A. (2004). Optical coherence tomography findings in myopic traction maculopathy. *Arch Ophthalmol* **122**, 1455-1460.

Paunescu, L. A., Schuman, J. S., Price, L. L., *et al.* (2004). Reproducibility of nerve fiber thickness, macular thickness, and optic nerve head measurements using StratusOCT. *Invest Ophthalmol Vis Sci* **45**, 1716-1724.

Percival, S. P. (1987). Redefinition of high myopia: the relationship of axial length measurement to myopic pathology and its relevance to cataract surgery. *Developments in ophthalmology* **14**, 42-46.

Perkins, E. S. (1979). Morbidity from myopia. *The Sight-saving review* **49**, 11-19.

Pierro, L., Camesasca, F. I., Mischi, M. and Brancato, R. (1992). Peripheral retinal changes and axial myopia. *Retina* **12**, 12-17.

Podoleanu, A., Charalambous, I., Plesea, L., Dogariu, A. and Rosen, R. (2004). Correction of distortions in optical coherence tomography imaging of the eye. *Physics in medicine and biology* **49**, 1277-1294.

Pokharel, G. P., Negrel, A. D., Munoz, S. R. and Ellwein, L. B. (2000). Refractive Error Study in Children: results from Mechi Zone, Nepal. *Am J Ophthalmol* **129**, 436-444.

Pollack, A. L. and Brodie, S. E. (1998). Diagnostic yield of the routine dilated fundus examination. *Ophthalmology* **105**, 382-386.

Ponte, F., Giuffre, G., Giammanco, R. and Dardanoni, G. (1994). Risk factors of ocular hypertension and glaucoma. The Casteldaccia Eye Study. *Doc Ophthalmol* **85**, 203-210.

Puliafito, C. A. and Baumal, C. A. (2000). Ocular Surgery News 8/15/00 issue OSN Supersite (http://www.osnsupersite.com/view.asp?ID=1310).

Quek, T. P., Chua, C. G., Chong, C. S., *et al.* (2004). Prevalence of refractive errors in teenage high school students in Singapore. *Ophthalmic Physiol Opt* **24**, 47-55.

Ramrattan, R. S., Wolfs, R. C., Jonas, J. B., Hofman, A. and De Jong, P. T. (1999). Determinants of optic disc characteristics in a general population: The Rotterdam Study. *Ophthalmology* **106**, 1588-1596.

Revelli, E. J., Lambreghts, K. and Barker, F. M. (2005a). A Multi-Center, Open, Non-Randomized Comparison Trial of Standard and Steered Optomap Retinal Exam and Binocular Indirect Ophthalmoscopy. *Invest. Ophthalmol. Vis. Sci.* **46**, 3282-.

Revelli, E. J., Lambreghts, K. and Barker, F. M. (2005b). A multi-center, open, non-randomized comparison trial of standard and steered Optomap retinal exam and binocular indirect ophthalmoscopy. *Invest. Ophthalmol. Vis. Sci.* **46**, 3282.

Rose, K., Smith, W., Morgan, I. and Mitchell, P. (2001). The increasing prevalence of myopia: implications for Australia. *Clin Experiment Ophthalmol* **29**, 116-120.

Rose, K. A., Morgan, I. G., Ip, J., *et al.* (2008a). Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology* **115**, 1279-1285.

Rose, K. A., Morgan, I. G., Smith, W., Burlutsky, G., Mitchell, P. and Saw, S. M. (2008b). Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol* **126**, 527-530.

Rose, K. A., Morgan, I. G., Smith, W. and Mitchell, P. (2002). High heritability of myopia does not preclude rapid changes in prevalence. *Clin Experiment Ophthalmol* **30**, 168-172.

Rosner, M. and Belkin, M. (1991). A nation-wide study of myopia prevalence in Israel. Findings in a population of 312,149 young adults. *Metab Pediatr Syst Ophthalmol* **14**, 37-41.

Rosner, M., Treister, G. and Belkin, M. (1987). Epidemiology of retinal detachment in childhood and adolescence. *J Pediatr Ophthalmol Strabismus* **24**, 42-44.

Saw, S. M. (2006). How blinding is pathological myopia? *Br J Ophthalmol* **90**, 525-526.

Saw, S. M., Chua, W. H., Gazzard, G., Koh, D., Tan, D. T. and Stone, R. A. (2005a). Eye growth changes in myopic children in Singapore. *Br J Ophthalmol* **89**, 1489-1494.

Saw, S. M., Gazzard, G., Koh, D., *et al.* (2002a). Prevalence rates of refractive errors in Sumatra, Indonesia. *Invest Ophthalmol Vis Sci* **43**, 3174-3180.

Saw, S. M., Gazzard, G., Shih-Yen, E. C. and Chua, W. H. (2005b). Myopia and associated pathological complications. *Ophthalmic Physiol Opt* **25**, 381-391.

Saw, S. M., Katz, J., Schein, O. D., Chew, S. J. and Chan, T. K. (1996). Epidemiology of myopia. *Epidemiol Rev* **18**, 175-187.

Saw, S. M., Zhang, M. Z., Hong, R. Z., Fu, Z. F., Pang, M. H. and Tan, D. T. (2002b). Near-work activity, night-lights, and myopia in the Singapore-China study. *Arch Ophthalmol* **120**, 620-627.

Schellini, S. A., Durkin, S. R., Hoyama, E., *et al.* (2009). Prevalence of refractive errors in a Brazilian population: the Botucatu eye study. *Ophthalmic Epidemiol* **16**, 90-97.

Seet, B., Wong, T. Y., Tan, D. T., *et al.* (2001). Myopia in Singapore: taking a public health approach. *Br J Ophthalmol* **85**, 521-526.

Semes, L. (1991). Direct Ophthalmoscopy. In: *Clinical procedures in optometry* (eds J. B. Eskridge, J. F. Amos and J. D. Bartlett), Lippincott, Philadelphia, pp 238-241.

Shih, Y. F., Ho, T. C., Hsiao, C. K. and Lin, L. L. (2006). Visual outcomes for high myopic patients with or without myopic maculopathy: a 10 year follow up study. *Br J Ophthalmol* **90**, 546-550.

Shimizu, N., Nomura, H., Ando, F., Niino, N., Miyake, Y. and Shimokata, H. (2003). Refractive errors and factors associated with myopia in an adult Japanese population. *Jpn J Ophthalmol* **47**, 6-12.

Shukla, M. and Ahuja, O. P. (1981). A possible relationship between lattice and snail track degenerations of the retina. *Am J Ophthalmol* **92**, 482-485.

Siderov, J. and Nurse, S. (2005). The mydriatic effect of multiple doses of tropicamide. *Optom Vis Sci* **82**, 955-958.

Smith, E. L., 3rd and Hung, L. F. (1999). The role of optical defocus in regulating refractive development in infant monkeys. *Vision research* **39**, 1415-1435.

Smith, E. L., Hung, L. F., Huang, J., Blasdel, T. L., Humbird, T. L. and Bockhorst, K. H. (2010). Optical Defocus Influences Refractive Development in Monkeys via Local, Regionally Selective Mechanisms. *Investigative ophthalmology & visual science*.

Snell, R. S. and Lemp, M. A. (1998). Ch. 7 The anatomy of the eyeball as seen with the ophthalmoscope, slit Lamp, and gonioscope In: *Clinical anatomy of the eye* (eds R. S. Snell and M. A. Lemp), pp 214-231.

Sperduto, R. D., Seigel, D., Roberts, J. and Rowland, M. (1983). Prevalence of myopia in the United States. *Arch Ophthalmol* **101**, 405-407.

Stone, R. A. and Khurana, T. S. (2010). Gene profiling in experimental models of eye growth: clues to myopia pathogenesis. *Vision Res* **50**, 2322-2333.

Strang, N. C., Winn, B. and Bradley, A. (1998). The role of neural and optical factors in limiting visual resolution in myopia. *Vision Res* **38**, 1713-1721.

Swann, P. and Schmid, K. (2002a). Fundus changes in myopia - an overview. *Optometry today*.

Swann, P. and Schmid, K. (2002b). Fundus changes in myopia - an overview. *Optometry Today* **42**, 33-35.

Tan, N. W., Saw, S. M., Lam, D. S., Cheng, H. M., Rajan, U. and Chew, S. J. (2000). Temporal variations in myopia progression in Singaporean children within an academic year. *Optom Vis Sci* **77**, 465-472.

Tano, Y. (2002). Pathologic myopia: where are we now? *Am J Ophthalmol* **134**, 645-660.

Tarasewicz, D. G. and Chan, C. K. (2006). Chapter 14 Peripheral Retinal Degenerative Lesions. In: *Handbook of Ophthalmology* (ed A. Agarwal), SLACK, Thorofare, NJ, pp 477-488.

Tekiele, B. C. and Semes, L. (2002). The relationship among axial length, corneal curvature, and ocular fundus changes at the posterior pole and in the peripheral retina. *Optometry* **73**, 231-236.

Ting, P. W., Lam, C. S., Edwards, M. H. and Schmid, K. L. (2004). Prevalence of myopia in a group of Hong Kong microscopists. *Optom Vis Sci* **81**, 88-93.

Tokoro, T. (1998). *Atlas of posterior fundus changes in pathologic myopia*. Springer, Tokyo.

Tong, L., Saw, S. M., Chua, W. H., *et al.* (2004). Optic disk and retinal characteristics in myopic children. *Am J Ophthalmol* **138**, 160-162.

Tsai, C. Y., Chang, T. J., Kuo, L. L., Chou, P. and Woung, L. C. (2007). Visual outcomes and associated risk factors of cataract surgeries in highly myopic Taiwanese. *Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology* **221**, 18-23.

Tse, D. Y., Lam, C. S., Guggenheim, J. A., *et al.* (2007). Simultaneous defocus integration during refractive development. *Invest Ophthalmol Vis Sci* **48**, 5352-5359.

Villarreal, G. M., Ohlsson, J., Cavazos, H., Abrahamsson, M. and Mohamed, J. H. (2003). Prevalence of myopia among 12- to 13-year-old schoolchildren in northern Mexico. *Optom Vis Sci* **80**, 369-373.

Villarreal, M. G., Ohlsson, J., Abrahamsson, M., Sjostrom, A. and Sjostrand, J. (2000). Myopisation: the refractive tendency in teenagers. Prevalence of myopia among young teenagers in Sweden. *Acta Ophthalmol Scand* **78**, 177-181.

Vitale, S., Sperduto, R. D. and Ferris, F. L., 3rd (2009). Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol* **127**, 1632-1639.

Vongphanit, J., Mitchell, P. and Wang, J. J. (2002). Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology* **109**, 704-711.

Wakitani, Y., Sasoh, M., Sugimoto, M., Ito, Y., Ido, M. and Uji, Y. (2003). Macular thickness measurements in healthy subjects with different axial lengths using optical coherence tomography. *Retina* **23**, 177-182.

Wang, N. K., Chen, Y. P., Lai, C. C., *et al.* (2009a). Paediatric retinal detachment: comparison of high myopia and extreme myopia. *Br J Ophthalmol* **93**, 650-655.

Wang, N. K., Tsai, C. H., Chen, Y. P., *et al.* (2005). Pediatric rhegmatogenous retinal detachment in East Asians. *Ophthalmology* **112**, 1890-1895.

Wang, Q., Klein, B. E., Klein, R. and Moss, S. E. (1994). Refractive status in the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* **35**, 4344-4347.

Wang, T. J., Chiang, T. H., Wang, T. H., Lin, L. L. and Shih, Y. F. (2009b). Changes of the ocular refraction among freshmen in National Taiwan University between 1988 and 2005. *Eye (London, England)* **23**, 1168-1169.

Webb, R. H., Hughes, G. W. and Pomerantzeff, O. (1980). Flying spot TV ophthalmoscope. *Applied Optics* **19**, 2991-2997.

Wensor, M., Mccarty, C. A. and Taylor, H. R. (1999). Prevalence and risk factors of myopia in Victoria, Australia. *Arch Ophthalmol* **117**, 658-663.

Wolsley, C. J., Saunders, K. J., Silvestri, G. and Anderson, R. S. (2008). Investigation of changes in the myopic retina using multifocal electroretinograms, optical coherence tomography and peripheral resolution acuity. *Vision Res* **48**, 1554-1561.

Wong, T. Y., Foster, P. J., Hee, J., *et al.* (2000). Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Invest Ophthalmol Vis Sci* **41**, 2486-2494.

Wong, T. Y., Foster, P. J., Johnson, G. J. and Seah, S. K. (2002). Education, socioeconomic status, and ocular dimensions in Chinese adults: the Tanjong Pagar Survey. *Br J Ophthalmol* **86**, 963-968.

Wong, T. Y., Klein, B. E., Klein, R., Knudtson, M. and Lee, K. E. (2003). Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology* **110**, 211-217.

Wong, T. Y., Klein, B. E., Klein, R., Tomany, S. C. and Lee, K. E. (2001). Refractive errors and incident cataracts: the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* **42**, 1449-1454.

Wu, H. M., Seet, B., Yap, E. P., Saw, S. M., Lim, T. H. and Chia, K. S. (2001). Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. *Optom Vis Sci* **78**, 234-239.

Wu, M. M. and Edwards, M. H. (1999). The effect of having myopic parents: an analysis of myopia in three generations. *Optom Vis Sci* **76**, 387-392.

Wu, S. Y., Nemesure, B. and Leske, M. C. (1999). Refractive errors in a black adult population: the Barbados Eye Study. *Invest Ophthalmol Vis Sci* **40**, 2179-2184.

Xu, L., Wang, Y., Li, Y., Cui, T., Li, J. and Jonas, J. B. (2006). Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology* **113**, 1134 e1131-1111.

Yap, M., Cho, J. and Woo, G. (1990). A survey of low vision patients in Hong Kong. *Clin Exp Optom* **73**, 19-22.

Younan, C., Mitchell, P., Cumming, R. G., Rochtchina, E. and Wang, J. J. (2002). Myopia and incident cataract and cataract surgery: the blue mountains eye study. *Invest Ophthalmol Vis Sci* **43**, 3625-3632.

Young, T. L. (2004). Dissecting the genetics of human high myopia: a molecular biologic approach. *Transactions of the American Ophthalmological Society* **102**, 423-445.

Young, T. L., Metlapally, R. and Shay, A. E. (2007). Complex trait genetics of refractive error. *Arch Ophthalmol* **125**, 38-48.

Young, T. L., Ronan, S. M., Alvear, A. B., *et al.* (1998a). A second locus for familial high myopia maps to chromosome 12q. *American journal of human genetics* **63**, 1419-1424.

Young, T. L., Ronan, S. M., Drahozal, L. A., *et al.* (1998b). Evidence that a locus for familial high myopia maps to chromosome 18p. *Am J Hum Genet* **63**, 109-119.

Yura, T. (1998). The relationship between the types of axial elongation and the prevalence of lattice degeneration of the retina. *Acta Ophthalmol Scand* **76**, 90-95.

Zejmo, M., Forminska-Kapuscik, M., Pieczara, E., *et al.* (2009a). Etiopathogenesis and management of high myopia. Part II. *Med Sci Monit* **15**, RA252-255.

Zejmo, M., Forminska-Kapuscik, M., Pieczara, E., *et al.* (2009b). Etiopathogenesis and management of high-degree myopia. Part I. *Med Sci Monit* **15**, RA199-202.

Zhang, Q., Guo, X., Xiao, X., Jia, X., Li, S. and Hejtmancik, J. F. (2006). Novel locus for X linked recessive high myopia maps to Xq23-q25 but outside MYP1. *Journal of medical genetics* **43**, e20.

Zhang, Z., Wang, J., Niu, W., *et al.* (2011). Corneal asphericity and its related factors in 1052 Chinese subjects. *Optom Vis Sci* **88**, 1232-1239.

Zhao, J., Pan, X., Sui, R., Munoz, S. R., Sperduto, R. D. and Ellwein, L. B. (2000). Refractive Error Study in Children: results from Shunyi District, China. *Am J Ophthalmol* **129**, 427-435.

Zundane, I., Massin, P., Erginay, A., Gaudric, A., Tadayoni, R. and Haouchine, B. (2005). Is OCT 3 Fast Macular Map as Reliable as Conventional Macular Map. *Invest. Ophthalmol. Vis. Sci.* **46**, 1547-.

Appendix

Subject History Checklist

1. Have you done any eye surgery before? **Yes / No**
    i. Which eye? Or both eyes?
    ii. What type of surgery is it?
    iii. How many times of surgery?
    iv. When have you done that?
2. Have you experienced any eye trauma? **Yes / No**
    i. Which eye? Or both eyes?
    ii. What is the cause of trauma?
    iii. How many times of trauma?
    iv. When did it happen?
3. Have you experienced any eye injury? **Yes / No**
    i. Which eye? Or both eyes?
    ii. What is the cause of injury?
    iii. How many times of injury?
    iv. When did it happen?
4. When did you find (the Sx) having myopia? (ask Sx's parent) **____yr old**
5. Do you live in Hong Kong since birth? **Yes / No**
6. Are you Chinese? **Yes / No**
7. Do you have any eye problem or eye disease you know? **Yes / No**
    (Including high myopia, squint, amblyopia, glaucoma, cataract, macular degeneration, retinal problem)
    i. Which eye? Or both eyes?
    ii. What is the eye problem / disease?
    iii. Is your eye recovered?
    iv. When did you have that eye problem / disease?
8. Do you have any floaters? **Yes / No**
    i. Which eye? Or both eyes?
    ii. When did you have that eye problem / disease?
    iii. Is the condition stable or happened in a sudden?
    iv. What is the color of the floaters?
    v. How many floaters are there? Few or a lot?

9. Do you experienced any flashes symptom? **Yes / No**
    i. Which eye? Or both eyes?
    ii. When did you have flashes?
    iii. What is the frequency of flashes?
    iv. Is there any symptoms associated?
10. Does your family have any eye problem? **Yes / No**
    (Including high myopia, squint, amblyopia, glaucoma, cataract, macular degeneration, retinal problem.)
    i. Which eye? Or both eyes?
    ii. What is the eye problem / disease?
    iii. Is your eye recovered?
    iv. When did you have that eye problem / disease?
11. Have your family members done any eye surgery before? **Yes / No**
    i. Which eye? Or both eyes?
    ii. What type of surgery is it?
    iii. How many times of surgery?
    iv. When have you done that?
12. Have you any health problem? **Yes / No**
    (Including DM, HT, heart, renal, or liver problem.)
    i. What is the problem / disease?
    ii. Have you recovered?
    iii. When did you have that problem?
13. Do your family members have any health problem? **Yes / No**
    (Including DM, HT, heart, renal, or liver problem.)
    i. What is the problem / disease?
    ii. Have you recovered?
    iii. When did he /she have that problem?
14. Do you have any allergy? **Yes / No**
    i. Which type of allergy is it?
15. Do you need to take medication regularly? **Yes / No**
    i. What is the medication?
16. When is your last eye examination? **_____ yr(s)**
17. How old is your current prescription? **_____ yr(s)**