Original Article/นิพนธ์ต้นฉบับ

การวิเคราะห์ต้นทุน-ประสิทธิผลของการตรวจคัดกรองพยาธิสภาพจอประสาทตาจากโรคเบาหวานในผู้ป่วยเบาหวานชนิดที่ 2

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บทคัดย่อ

วัถตุประสงค์: เพื่อประเมินต้นทุน-ประสิทธิผลของความถี่ต่างๆ ของการตรวจคัดกรองพยาธิสภาพจอประสาทตาผู้ป่วยเบาหวานชนิดที่ 2 ด้วยเครื่องมือ Indirect ophthalmoscopy โดยจักษุแพทย์ ในมุมมองของโรงพยาบาล

ระเบียบวิธีวิจัย: การศึกษานี้ใช้โครงสร้างแบบจำลองโรคชนิดมาร์คอฟ โดยทำการติดตามผู้ป่วยเบาหวานชนิดที่ 2 ที่เพิ่งได้รับการวินิจฉัยจำนวน 1,000 คน โดยติดตามตั้งแต่อายุ 40 ปีจนอายุ 75 ปีหรือเสียชีวิต ค่าความน่าจะเป็นในการเปลี่ยนจากสถานะสุขภาพหนึ่งไปสู่สถานะสุขภาพหนึ่งได้จากการทบทวนวรรณกรรมและผู้เชี่ยวชาญ สำหรับข้อมูลต้นทุนได้รับจากโรงพยาบาลซึ่งเป็นโรงเรียนแพทย์แห่งหนึ่งในจังหวัดกรุงเทพมหานคร การคำนวณต้นทุนใช้วิธี microcosting ผลการศึกษานำเสนอเป็นเงินบาทที่เพิ่มขึ้นต่อการป้องกันตาบอด 1 ดวง (incremental Baht per blindness prevented) การศึกษานี้ใช้อัตราค่าปรับลดเท่ากับร้อย 3 การศึกษานี้มีการวิเคราะห์ความไวหลายชนิด

ผลการศึกษา: ผลการศึกษาพบว่าอัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลในกลุ่มผู้ป่วยที่ได้รับการตรวจคัดกรองทุก 4 และ 3 ปีเปรียบเทียบกับกลุ่มผู้ป่วยที่ไม่ได้รับการตรวจคัดกรองมีค่าสูงกว่าค่าอัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลในกลุ่มผู้ป่วยที่ได้รับการตรวจคัดกรองทุก 2 ปีเมื่อเปรียบเทียบกับกลุ่มผู้ป่วยที่ไม่ได้รับการตรวจคัดกรอง ภาวะนี้ค่าอัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลที่สูงเช่นนี้ทำให้การตรวจคัดกรองทุก 4 และ 3 ปีไม่มีความคุ้มค่าทางการแพทย์ อัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลในกลุ่มผู้ป่วยที่ได้รับการตรวจคัดกรองทุก 2 ปีเปรียบเทียบกับกลุ่มผู้ป่วยที่ไม่ได้รับการตรวจคัดกรอง มีค่าเท่ากับ 79,879 บาทต่อการป้องกันตาบอดได้หนึ่งดวง ในขณะที่อัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วย

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ประสิทธิผลในกลุ่มผู้ป่วยที่ได้รับการตรวจคัดกรองทุก 1 ปีเปรียบเทียบกับการคัดกรองทุก 2 ปี มีค่าเท่ากับ 95,225 บาท ต่อการป้องกันตาบอดได้หนึ่งดวง

ผลการวิเคราะห์ความไวพบว่า ถ้าต้นทุนของการตรวจคัดกรอง, ต้นทุนของการรักษาด้วยแสงเลเซอร์, โอกาสที่ผู้ไม่ได้รับการตรวจคัดกรองจะมาพบแพทย์ด้วยตนเอง, โอกาสที่ผู้ได้รับการตรวจคัดกรองจะได้รับการรักษาด้วยการผ่าตัดจอประสาทตาและอัตราการตายเพิ่มขึ้น จะทำให้อัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลเพิ่มขึ้น ถ้าการดำเนินโรค, ประสิทธิภาพของการรักษา, ความเสี่ยงของการเกิด Background Diabetic Retinopathy (BDR) เมื่อแรกเริ่มวินิจฉัยโรคเบาหวาน, อัตราการปรับลด, โอกาสที่ผู้ไม่ได้รับการตรวจคัดกรองจะได้รับการรักษาด้วยการผ่าตัดจอประสาทตา, ความไวและความจำเพาะของการตรวจคัดกรองเพิ่มขึ้นจะทำ ให้อัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลลดลง นอกจากนี้ยังพบว่าถ้าระดับน้ำตาลในผู้ป่วยที่ได้รับการตรวจคัดกรองลดลง จะส่งผลให้อัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผลลดลงอย่างมาก เมื่อวิเคราะห์ในมุมมองทางสังคม พบว่าการได้รับการตรวจคัดกรองจอประสาทตานั้นมีต้นทุนที่ต่ำกว่าและสามารถป้องกันตาบอดได้มากกว่าเมื่อเปรียบเทียบกับการไม่ได้รับการตรวจคัดกรอง

สรุปผล: การตรวจคัดกรองทุกปีช่วยป้องกันตาบอดได้ดีที่สุด แต่สำหรับผู้ป่วยที่มีความเสี่ยงต่ำ เช่น กลุ่มที่ควบคุมน้ำตาลได้ดี ไม่มีภาวะเบาหวานขึ้นตาในการตรวจครั้งก่อน การตรวจคัดกรองทุก 2 ปีน่าจะเหมาะสมกว่า ผลการศึกษาจากส่วนวิเคราะห์ความไวบ่งชี้ว่าต้นทุนการตรวจคัดกรองเป็นตัวแปรที่มีความสำคัญและมีผลต่อค่าอัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผล
จักษุเวชสาร 2553; มกราคม-มิถุนายน 24(1): 10-25.

Original Article/นิพนธ์ต้นฉบับ

Diabetic Retinopathy Modeling: Cost-effectiveness of Varying Screening Intervals in Type 2 Diabetes Mellitus in Thailand

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Abstract

Objective: To assess the cost-effectiveness of various screening intervals using indirect ophthalmoscopy performed by ophthalmologists for detecting diabetic retinopathy (DR) among type 2 diabetic patients from a hospital perspective.

Methodology: A Markov model was used for simulating a cohort of 10,000 newly diagnosed type 2 diabetic patients, who were followed from 40 years of age until the age of 75 years or death. Transition probabilities were derived from published literature and expert opinions. Cost data and utilization patterns were obtained from a teaching hospital located in Bangkok.

All cost estimates were calculated using a micro costing technique. Incremental cost-effectiveness analysis was performed and presented as incremental Baht per blindness prevented. A discount rate of 3% was used. A series of sensitivity analyses was performed.

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Results: The incremental cost-effectiveness ratios (ICER) comparing the group being screened every 4 years and for every 3 years with the no screening group were higher than the ICER of increased screening frequency from no screening to every 2 years. This extended dominance makes screening every 4 and 3 years to be not cost-effective. The ICER of increasing screening frequency from no screening to every 2 years was 79,879 Baht per additional blindness prevented. Finally, the ICER of increased screening frequency from every 2 years to annually was 95,225 Baht to prevent blindness per eye. For sensitivity analysis, if the cost of eye screening and laser treatment, probability of medical treatment seeking among unscreened patients, probability of screened patients being treated with vitrectomy, and annual mortality rate were increased, the ICER would be increased. If the progression of disease, effectiveness of treatment, the BDR risk at diagnosis of DM, discount rate, probability of unscreened patients being treated with vitrectomy, sensitivity of screening, and specificity of screening were increased, the ICER would be decreased. In addition, if the level of glycemic control among screened patients was incorporated in the model, the cost-effectiveness of screening would be increased dramatically. Additional analysis in societal perspective demonstrated that all screening intervals resulted in cost-savings.

Conclusions: Annual screening is the safest strategy for the prevention of blindness. However, for low risk groups (e.g., good glycemic control, no retinopathy on previous examination), every 2 years screening may be appropriate. The results from sensitivity analysis showed that the cost of screening examination was an important parameter affecting the ICER. **Thai J Ophthalmol 2010; January-June 24(1): 10-25.**

Keywords: Diabetic retinopathy screening, cost-effectiveness analysis

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Introduction

Diabetes Mellitus (DM) remains a profound health problem worldwide.[1] Diabetes is a significant public health problem in Thailand with a prevalence of 4-6%.[2] It was estimated that 17-37% of type 2 diabetics have diabetic retinopathy (DR) complications.[3-8] DR is a leading cause of visual impairment and blindness in patients with type 2 diabetes mellitus.[9] Blindness caused by diabetes is preventable by early detection of retinopathy, good timely laser treatment, and glycemic control.[9] Therefore, screening is vital for prevention of visual loss from DR.[10]

The American Diabetes Association (ADA) guideline recommends that patients with type 2 DM should have an eye examination at the time of diagnosis and annually afterwards.[11] However, adherence to the guidelines for annual ophthalmic examination is poor, ranging only from 34 to 65 percent.[12-13] Even among diabetic patients at high risk for vision loss because of pre-existent DR or long duration of diabetes, the rates of adherence were only 61 and 57 percent, respectively.[12] Several studies evaluating the cost-effectiveness of screening with varying intervals indicated that screening less often than annually is more cost-effective.[10,14-15]

Although annual screening for DR is recommended, the limited resources available in Thailand make it difficult to provide eye examinations in all DM patients. Moreover, an increasing frequency of DR screening has been found to be associated with increasing costs. However, no such study was conducted in Thailand before. The aim of this study is to assess the cost-effectiveness of various screening intervals using indirect ophthalmoscopy performed by ophthalmologists for detecting DR among type 2 diabetic patients from a hospital perspective.

Methods

Diabetic retinopathy model

A model was developed using the Markov technique (a computer program, Microsoft Excel spreadsheet version 97). The model was constructed based on the Eastman Diabetes Model.[16-17] A cohort of 10,000 newly diagnosed, type 2 diabetic patients age 40 years was simulated until the age of 75 years or death. Simulated patients were classified based on NDR (no diabetic retinopathy), BDR or NPDR (background diabetic retinopathy or nonproliferative diabetic retinopathy), PDR (proliferative diabetic retinopathy), ME (macular edema), and blindness (visual acuity worse than 20/100 in the better eye). The model assumed that retinopathy did not regress and that progression was sequential. The model structure is shown in Figure 1.

Transition probability

Transition probabilities (tp) were derived from Eastman et al,[17] Javitt et al,[14,19-20] and WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy).[18] The transition probabilities are outlined in Table 1. Based on Eastman et al., risk of BDR was estimated to be about 20 percent at diagnosis of type 2 DM.[17,21] The transition probabilities (tp1, tp2, tp3) used in this study were updated by using the 10 year WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy),[18] instead of 4-year incidence data used in the Eastman Model.[17] These probabilities of developing DR varied by duration of diabetes. As shown in Table 1, the rates of progression from PDR or ME (macular edema) to Blindness were derived from Javitt et al,[14] and Eastman et al.[17] Also, this progression rate was assumed to be decreased with laser treatment. Annual mortality rate for each state was calculated based on the annual mortality

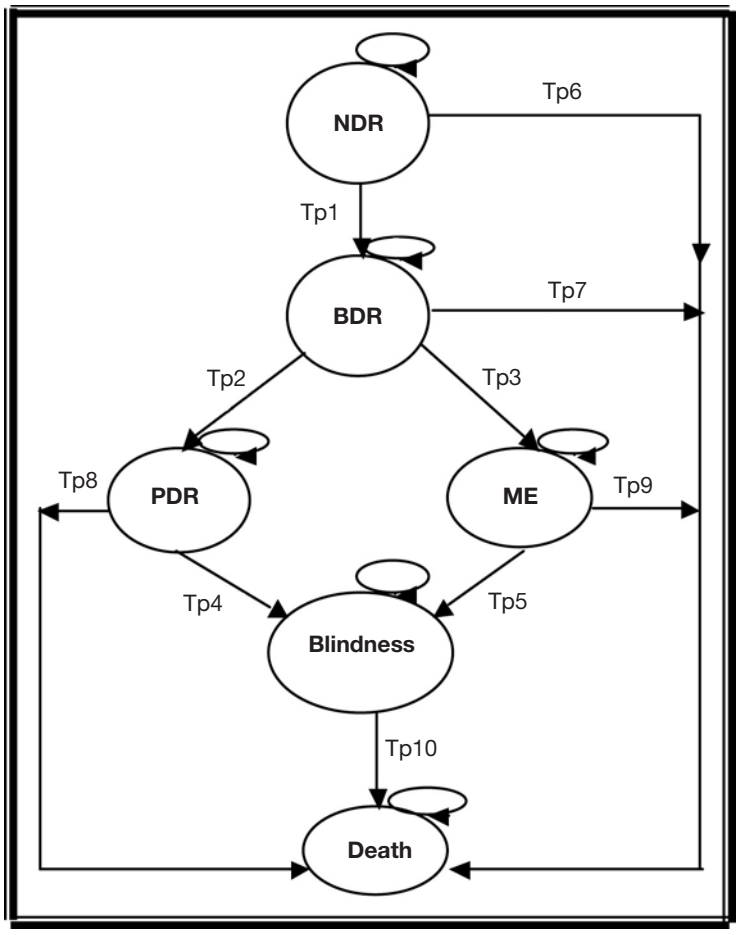

Figure 1. *The simulation model of DR*

risk in type 2 DM with DR and the age-specific mortality in type 2 DM.[14,19,24] Age-specific mortality rate was based on Thai population data.

Cost model

Unit cost and utilization patterns were obtained from a teaching hospital located in Bangkok. All cost estimates were calculated using a microcosting technique. Only direct medical costs were used in the model. These costs consisted of eye screening examination cost, treatment cost, and follow-up cost.

Eye screening examination consisted of visual acuity examination, eye dilatation, anterior segment examination, intraocular pressure examination, and fundoscopic eye examination (with indirect ophthalmoscopy). Cost of panretinal photocoagulation for treatment PDR, cost of focal or grid photocoagulation for ME, and vitrectomy are presented in Table 1.

This study constructed five different strategies of screening as the following: no screening, annual screening, every 2 years screening, every 3 years screening, and every 4 years screening. For all screening strategies, the first screening began at time of diagnosis of DM. The model assumed that all individuals with treatable retinopathy who were detected by screening would receive timely and appropriate treatment. The patients diagnosed with BDR remained untreated, however, they were

Table 1. Base-case parameters and assumptions

Parameters	Base-case analysis
Annual disease progression rates	
Progression from NDR to BDR (tp1)	
BDR risk present at diagnosis DM[17,21]	20%
1-4 year[18]	0.1479
5-9 year[18]	0.1596
10-14 year[18]	0.1241
15+ year[18]	0.0785
Progression from BDR to PDR (tp2)	
1-4 year[18]	0.0123
5-9 year[18]	0.0149
10-14 year[18]	0.0204
15+ year[18]	0.0257
Progression from BDR to ME (tp3)	
1-4 year[18]	0.0945
5-9 year[18]	0.1154
10-14 year[18]	0.1112
15+ year[18]	0.0840
Progression from PDR to Blindness (tp4)[17]	0.088
Progression from PDR to Blindness after treatment (tp4)[14,17]	0.0148
Progression from ME to Blindness (tp5)[14,17]	0.050
Progression from ME to Blindness after treatment (tp5)[14,17]	0.033
Annual mortality rate	
NDR (tp6)[14]	[6.2%+(2 x age-specific mortality)]/2
BDR (tp7)[14]	[9.1%+(2 x age-specific mortality)]/2
PDR (tp8)[14]	[11.5%+(5 x age-specific mortality)]/2
ME (tp9)[14]	[9.3%+(2 x age-specific mortality)]/2
Blindness (tp10)[14]	[19.9%+(5 x age-specific mortality)]/2
Screening test	
NDR called BDR[10,22]	0.05
NDR called PDR[10,22]	0.003
BDR called NDR[10,22]	0.22
BDR called PDR[10,22]	0.02
PDR called NDR[10,22]	0.02
PDR called BDR[10,22]	0.03
Sensitivity for ME[10,23]	0.82
Specificity for ME[10,23]	0.79

Table 1. Base-case parameters and assumptions *(cont.)*

Parameters	Base-case analysis
Costs (Baht)	
Eye screening examination	113.79
Panretinal photocoagulation (in group being screened)	2,333.41
Panretinal photocoagulation (in group being unscreened)	2,447.20
Focal /grid photocoagulation (in group being screened)	931.08
Focal /grid photocoagulation (in group being unscreened)	1,044.87
Vitrectomy (in group being screened)	20,825.61
Vitrectomy (in group being unscreened)	20,939.40
Follow-up for BDR	227.57
Follow-up for PDR	227.57
Follow-up for ME	227.57
Misdiagnosis of NDR or PDR called BDR	113.79
Misdiagnosis of NDR or BDR called PDR, and no ME called ME	98.03
Discount rate for present value analysis (per year)	3%
Others*	
Probability of medical treatment seeking among unscreened PDR	20%
Probability of medical treatment seeking among unscreened ME	50%
Probability that unscreened patients were treated with vitrectomy	40%
Probability that screened patients were treated with vitrectomy	

* Derived from expert opinions

assigned to a follow-up screening program by the ophthalmologist. The patients diagnosed with PDR or ME were treated with laser photocoagulation or vitrectomy. As the result of treatment, risk of blindness was reduced in treated patients. Then, these patients were assigned to a follow-up for twice per year. For the unscreened patients, some of them may also seek medical service without being diagnosed by screening strategy.

Sensitivity and specificity of the screening in detecting DR or diabetic maculopathy are shown in Table 1. In this study, the features of the screening were presented in a different way as compared to the traditional description. Instead of directly incorporating sensitivity and specificity in the model, we adopt a concept of categorizing the feature of screening as correct or incorrect diagnosis.[10] For example, those patients with BDR can be misdiagnosed as either NDR or PDR. In this case, the screening result could be 1) correct diagnosis as BDR, 2) BDR called NDR, or 3) BDR called PDR. In the model, if screening failed to detect DR (false negative), the patients would remain at risk for all complications of DR, but would not be eligible for treatment until disease was detected. If the screen result was a false positive, the cost associated with the false positive during screening was incorporated into the model. For example, if a patient with PDR was misdiagnosed as BDR, they were assigned to a follow-up screening by the ophthalmologists in the next year. Thus, cost for misdiagnosis incurred. After that the patient would receive laser treatment.

Cost for false positive (misdiagnosis cost) was incorporated into the model. Cost of false positive for a patient with NDR who was misdiagnosed as BDR was equal to the eye screening examination cost. Misdiagnosis cost for false positive if the patient with NDR or BDR was misdiagnosed as PDR or the patient without ME was misdiagnosed as ME was equal to the summation of visual acuity cost, eye dilatation cost, and fundoscopic eye examination cost (with laser). Cost incurred if the patient with PDR was misdiagnosed as BDR included eye screening examination cost (misdiagnosis cost), panretinal photocogulation cost and follow-up cost. Costs and blindness were discounted at 3 percent per year.

For unscreened diabetic patients, 20 percent of PDR patients and 50 percent of ME patients may seek medical care treatment by themselves. It was assumed that 92.5 percent of PDR patients in the screened groups were treated with laser photocoagulation, while 7.5 percent of them were treated with vitrectomy. It was assumed that 60 percent of PDR patients in the unscreened groups were treated with laser photocoagulation, while 40 percent of them were treated with vitrectomy. Patients in the group being unscreened were required to have eye examination before receiving treatment. Compliance to the screening, treatment procedure, and follow-up was assumed to be 100 percent.

Cost-effectiveness analysis and sensitivity analysis

Incremental cost-effectiveness analysis was performed and presented as incremental Baht per blindness prevented. A discount rate of 3% was used. A series of sensitivity analyses including one-way analysis and best-worst case was performed.

Results

Base-case analysis

In base-case analysis, the incremental cost-effectiveness ratio (ICER) of the screening intervals (annual screening, every 2 years screening, every 3 years screening, and every 4 years screening, as compared to the preceding screening frequency) was examined. It was found that after following a cohort of 10,000 patients, newly diagnosed with type 2 DM at age 40 years until they were 75 years old or dead, the cumulative incidence of blindness among annual screening, every 2 years screening, every 3 years screening, every 4 years screening, and no screening were 1,810 persons, 1,847 persons, 1,871 persons, 1,889 persons, and 1,977 persons respectively. The discounted cumulative incidence of blindness among annual screening, every 2 years screening, every 3 years screening, every 4 years screening, no screening were 1,757 persons, 1,793 persons, 1,816 persons, 1,834 persons, and 1,920 persons respectively (Figure 2).

As shown in Table 2, screening every 4 years or every 3 years was not cost-effective. Screening every 4 years was not cost-effective because of extended dominance demonstrated by the lower incremental cost-effectiveness ratio value (86,042 VS 81,674 Baht/blindness prevented for every 4 years compared to no screening and every 3 years compared to no screening, respectively). Extended dominance is also applied to screening every 3 years (81,674 VS 79,878 Baht/blindness prevented for every 3 years compared to no screening and every 2 years compared to no screening, respectively). The ICER of increasing screening frequency from no screening to every 2 years was 79,879 Baht per additional blindness prevented. Finally, the ICER of increasing screening frequency from every 2 years to annual was 95,225 Baht per additional blindness prevented.

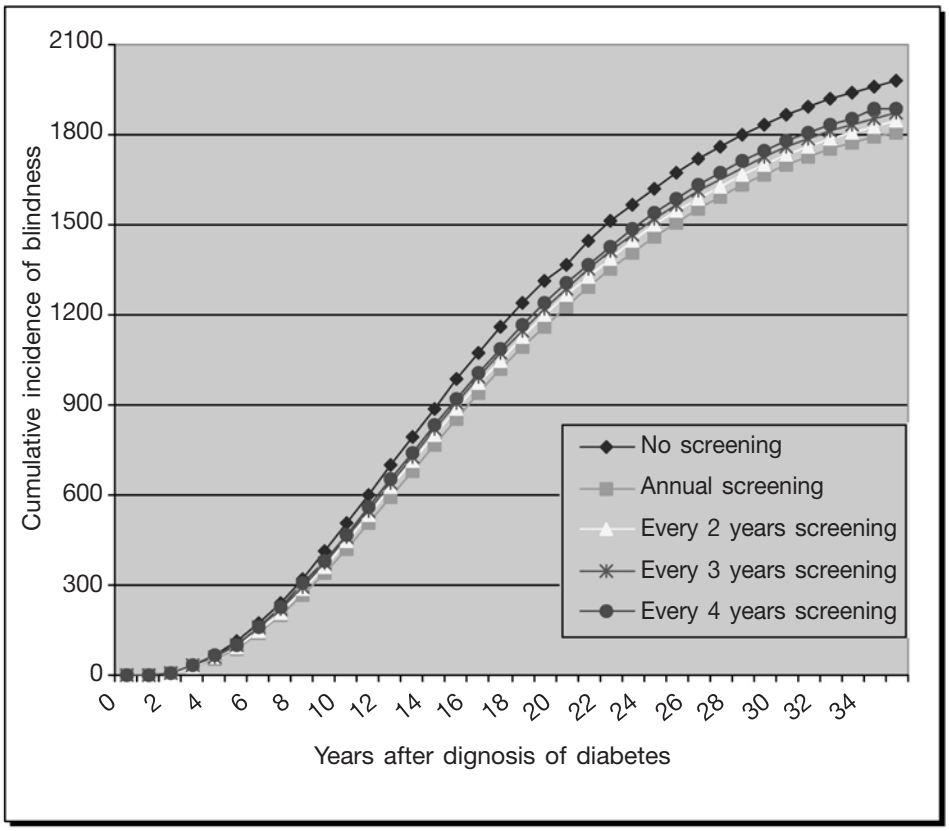

Figure 2. *Cumulative incidence of blindness among different screening interval groups (รูปสีท้ายเล่ม)*

Table 2. Incremental cost-effectiveness ratio of increased screening frequency in Thailand

Screening frequency*	**Total cost + (Baht)**	**Total blindness + (person)**	**Incremental cost-effectiveness ratio++ (Baht/additional blindness prevented)**
None	13,425,046.29	1,920	-
Every 4 years	20,824,736.62	1,834	Not cost-effective
Every 3 years	21,919,089.29	1,816	Not cost-effective
Every 2 years	23,569,641.06	1,793	79,878.70
Annual	26,997,752.90	1,757	95,225.33

* Population of homogeneous patients age 40 years, newly diagnosed as having type 2 diabetes mellitus.

\+ Total costs represents total costs associated with DR over 35 years after diagnosis; all costs and outcome (blindness) are discounted at 3%. The undiscounted number of persons with blindness was 1,977, 1,889, 1,871, 1,847, and 1,810 for no screening, every 4 years, every 3 years, every 2 years, and annual screening, respectively.

++ Incremental cost-effectiveness (compared with the preceding screening frequency; e.g. annual screening compared with every other year screening).

Sensitivity analysis

For sensitivity analysis, if the cost of eye screening, cost of laser treatment, probability of medical treatment seeking among unscreened patients, probability of screened patients being treated with vitrectomy, and annual mortality rate were increased, the ICER would be increased. If the progression of disease, effectiveness of treatment, the BDR risk at diagnosis of DM, discount rate, probability of unscreened patients being treated with vitrectomy, sensitivity of screening, and specificity of screening were increased, the ICER would be decreased. In addition, if the level of glycemic control among screened patients was incorporated in the model, the cost-effectiveness of screening would be increased dramatically. Additional analysis in societal perspective demonstrated that all screening intervals resulted in cost-savings.

Discussion

The aim of this study is to assess the cost-effectiveness of various screening intervals for diabetic retinopathy among type 2 diabetic patients in Thailand, using the Markov modeling technique. The results of this study revealed the incremental cost-effectiveness ratio (ICER) of annual screening, every 2 years screening, every 3 years screening, every 4 years screening, and no screening, as compared to the preceding screening frequency. As expected, it was found that the discounted incidence rate of blindness among the unscreened group was the highest, followed by the rates among every-4-years screening, every-3-years screening, every 2 years screening, and annual screening, respectively. On the other hand, the cost incurred for annual screening was the highest, followed by the costs among every 2 years screening, every-3-years screening, every-4-years, and no screening.

The ICER comparing the group being screened every 4 years to the group being unscreened found and also the ICER comparing the group being screened every 3 years to the group being screened every 4 years were found to be extended dominant by screening every 2 years.

The ICER comparing the group being screened every 2 years to the group being unscreened costs about 79,879 Baht per additional blindness prevented. Finally, the ICER comparing the group being screened annually to the group being screened every 2 years found that it costs about 95,225 Baht per additional blindness prevented. The result of this study was different from that of Vijan et al.[10] Vijan et al.[10] found that retinal screening annually vs. every 2 years for patients with type 2 diabetes costs $ 107,510 per QALY (quality-adjusted life-years) gained, while screening every 2 years vs. every 3 years costs $ 49,760 per QALY gained, every 3 years vs. every 5 years costs $ 30,160 per QALY gained, and that consideration should be given to increasing the screening interval. While our findings indicated that the incremental cost incurred from increasing frequency intervals was less than 100,000 Baht, it cost at least $ 16,790 per QALY gained in Vijan et al.[10] Besides the fact that Vijan et al.[10] conducted cost utility analysis and their cost of treatment and screening were much higher than those used in our study, four differences between their assumptions and our assumptions should be discussed. First, rates of progression of Vijan et al.[10] were stratified by age and level of glycemic control. Second, the unscreened patients in Vijan's study[10] did not seek medical treatment for PDR or ME. Thus the cost was not incurred among the unscreened group. Third, hypothetical patients in Vijan et al.[10] were based on the United States population of diabetic patients. Finally, cost of treatment in Vijan et al.[10] was only the cost of laser photocoagulation. No cost of vitrectomy was included in Vijan's model.

It was found that the incremental cost incurred from increasing frequency in all screening intervals was less than 100,000 Baht. In addition, all screening intervals resulted in cost saving when indirect cost was taken into account. Annual screening can prevent the largest number of blindnesses. However, annual screening may lead to higher costs and require a lot of ophthalmologists. Although annual screening seems to be cost-effective it may not be practical to screen for DR annually due to the limited resources both in terms of budget and the number of the ophthalmologists. Our study suggested that annual screening is the safest strategy to prevent blindness. However, for low risk groups (e.g., good glycemic control, no retinopathy on previous examination), every 2 years screening may be appropriate. The results from sensitivity analysis showed that the cost of the screening examination was an important parameter affecting the ICER. In addition, labor cost was found to be the highest proportion of the cost of screening. Based on the fact that labor cost for eye screening is the biggest part of cost of eye screening and that there are insufficient ophthalmologists, training other health personnel for DR screening technique or use of other techniques may be needed to better manage DR in the presence of inadequate resources. For example, health officer and health volunteers should be trained in visual acuity measurement and provision of health education about DR. Nurses and physicians at the district level should be trained particularly to measure visual acuity and to use ophthalmoscopy to screen for DR. Ophthalmic nurses and ophthalmologists at the provincial level should be trained to supervise and communicate with health care personnel in other levels. In addition, care of people with diabetes requires a multidisciplinary team with active participation of the patients. The physicians and ophthalmologists should carefully advise the diabetic patients regarding the importance of routine eye examinations and good glycemic control to decrease the progression of DR.

Since mortality in diabetic patients is influenced by the development of complications, cardiovascular diseases are the leading causes of mortality in type 2 DM.[25] In addition, nephropathy complication is frequently an underlying cause in death.[25] In previous studies, Javitt et al.[14,19] assigned a person-years of sight saved for the outcome, while Vijan et al.[10] assessed the value of blindness in terms of quality-adjusted life-years (QALYs). Although the presence of more severe retinopathy or visual impairment in diabetics patients is an indicator for increased risk of heart disease death,[26] retinopathy, itself, had a small impact on increased mortality risk, as compared to other complications. Also, there is an absence of the utility value for each state of DR in Thailand. Thus, the ICER, assessed as the ratio of the net increase in health care costs to the net increase in blindness prevented in this study, would be justified.

When looking at the assumptions used in the study, there are three main differences from the previous studies.[10,14,17,27-28] First, the transition probabilities from NDR to BDR (tp1), BDR to PDR (tp2), and BDR to ME (tp3) used in this study were varied with the disease duration of diabetes while the probabilities used in the previous studies[14,17,27-28] were assumed to be linear. Second, some of the unscreened patients in this study were assumed to seek medical treatment for PDR or ME by themselves, which is consistent with the real situation. Finally, the probability of patients being treated with laser photocoagulation and vitrectomy among screened patients and unscreened patients was incorporated in the model.

The benefits of screening can be explained by several reasons. First, patients receiving screening will be diagnosed earlier and treated properly. As a result, those patients will have slower rate of progression to blindness[11,29] as compared to those

who are not screened. In this study, we have incorporated this fact into the model by using different probabilities of progression from PDR to blindness and from ME to blindness between unscreened patients and screened patients. In addition, the risks of blindness among patients with PDR or ME, who received treatment were assumed to be decreased. [14,17] The other benefits of screening that were not incorporated in base-case analysis are the benefit of screening on glycemic control and on other eye diseases.

The screening may result in an increased awareness for glycemic control. Those who received screening may increase their effort to control their blood glucose to prevent DR. In addition, clinicians may use aggressive treatment in an attempt for better blood glucose control when the eye examination results indicate the progression of DR. When the effect of glycemic control from screening was incorporated in the model, it was found that the ICER would be decreased dramatically from the base-case analysis. The benefit of glycemic control as derived from Eastman's method[16] was higher than that of Vijan's method.[10] It might be the case that glycemic control from Eastman's method[16] had an impact on tp1,tp2, and tp3, while effect of glycemic control derived from Vijan's method[10] affected only tp1. In addition, eye screening examination for DR would not only detect DR but would also detect several other eye diseases. However, this benefit was not incorporated in the model.

Screening may also have several disadvantages. First, it may cause anxiety among people who are falsely classified as having disease. In addition, for those whose results were false negative, these people would still remain at risk for DR.

For sensitivity analysis, the impacts of each parameter were examined. As expected, if the cost of eye screening, or cost of laser treatment, or probability of medical treatment seeking among unscreened, or probability of screened patients being treated with vitrectomy, or annual mortality rate were increased, the ICER would be increased. Consistent with the real situation, if the progression of disease, effectiveness of treatment, or the BDR risk at diagnosis of DM, or discount rate, or cost of vitrectomy, or probability of unscreened patients being treated with vitrectomy, or sensitivity of screening, or specificity of screening were increased, the ICER would be decreased. In addition, if the level of glycemic control among screened patients was incorporated in the model, the cost-effectiveness of screening would be increased dramatically. When the indirect cost was taken into account, all screening intervals would result in cost saving. The indirect costs used in sensitivity analysis were calculated from GDP (gross domestic product) per capita. However, it can be calculated by other methods such as interviewing the patients, or using information on minimum wage per day. In addition, for blinded patients aged over 60 years old, no indirect cost was calculated since they were assumed to be retired. However, these patients could have a job in the real situation.

The results from one-way sensitivity analysis also indicated that tp1, tp2, effect of glycemic control, cost of screening,had intense impact on the ICER. Therefore, the validity of these parameters should be examined carefully.

For best-worst analysis, the results from best-case analysis ranged from 96.61-98.81 percent from the base-case analysis. On the other hand, the results from worst-case analysis ranged from 1,551.87-2,372.51 percent from the base-case analysis. In the worst scenario, it might not be cost-effective for screening thus the ICER of screening was increased dramatically.

Several limitations of this study should be

addressed. First, the compliance rates of treatment, follow-up program, and screening were assumed to be 100 percent. In addition, all of the patients who were diagnosed with PDR or ME from screening were assumed to receive treatment. These assumptions may not be true in the real situation. If the compliance and rate of receiving treatment among screened groups were decreased, the ICER would be increased from the base-case analysis.

Second, the benefits of screening may be underestimated since the DR screening may result in earlier detection of other eye diseases including cataract and glaucoma. However, this benefit was not included in the model. If this benefit were incorporated in the model, the ICER would be decreased, resulting in the increase of cost-effectiveness of the screening. Third, in this study, it was assumed that the progression to the next health state was irreversible. In the real situation, if the patients with BDR had good glycemic control, they would regress from BDR back to NDR.[30] However, the benefit of good glycemic control resulting in the slower rate of DR progression was examined in the sensitivity analysis.

Fourth, this study was conducted in the hospital perspective, therefore, the indirect cost was not included. From the societal perspective, when the indirect cost was included, the benefits of screening would outweigh its cost for all screening intervals, as shown in sensitivity analysis.

Fifth, this study did not include the state of having PDR and ME simultaneously in the model. Even though this state may occur in the real situation it was not documented as a state in several previous studies[14,17,28,31] resulting in difficulty in obtaining the correct transition probabilities from PDR state or ME state to PDR and ME state, or PDR and ME state to Blindness. For this reason, the structure of the model did not include the state of PDR and ME, which is similar to the previous studies.[14,17,28,31] In addition, the PDR and ME state were assumed to be a subset of the PDR state in this study.

Sixth, the disease modeling in this study estimated the long-term benefit of screening based on the available data. In the absence of information from Thailand, the parameters used in the model were derived mostly from studies conducted in the Western countries and from expert opinions. However, these parameters were validated by ophthalmologists in Thailand. In addition, information on costs including cost of treatment and screening were obtained from one university hospital in Bangkok. It may not be applicable for other hospitals. However, in sensitivity analysis, the cost of treatment and screening were varied to determine its impact on ICER result. Also, the cost of vitrectomy in this study was an average cost of Pars Plana Vitrectomy (PPV) with endolaser, PPV with prefluoron, PPV with silicone oil injection, and PPV with DK line. However, it should be calculated using the actual proportion of utilization of each method. Seventh, patients who had PDR or ME were assumed to receive one course of laser photocoagulation or one time of vitrectomy. However, in the real situation, more than one course of laser photocoagulation or one time of vitrectomy may be required.

Finally, the hypothetical patients used in the model were 10,000 newly diagnosed with type 2 DM, age 40 years old with HbA1C 10%. These patients were followed until the age of 75 years old or death, whichever occurred first. Therefore, the generalizibility of this result to different groups of patients should be made with caution.

Conclusion

Annual screening is the safest strategy for the prevention of blindness. However, for low risk groups (e.g., good glycemic control, no retinopathy on

previous examination), every 2 years screening may be appropriate. Policy makers and clinicians may want to consider the use of these research findings to aid decision making regarding the recommended frequency for diabetic retinopathy screening in Thailand.

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