

# Incidence and Progression of Diabetic Retinopathy During 17 Years of a Population-Based Screening Program in England

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**OBJECTIVE**—To estimate the incidence of diabetic retinopathy in relation to retinopathy grade at first examination and other prognostic characteristics.

**RESEARCH DESIGN AND METHODS**—This was a dynamic cohort study of 20,686 people with type 2 diabetes who had annual retinal photography up to 14 times between 1990 and 2006. Cumulative and annual incidence rates were estimated using life tables, and risk factors for progression were identified using Cox regression analysis.

**RESULTS**—Of 20,686 patients without proliferative diabetic retinopathy (PDR) or sight-threatening maculopathy at their first retinal examination (baseline), 16,444 (79%) did not have retinopathy, 3,632 (18%) had nonproliferative retinopathy, and 610 (2.9%) had preproliferative retinopathy. After 5 years, few patients without retinopathy at baseline developed preproliferative retinopathy (cumulative incidence 4.0%), sight-threatening maculopathy (0.59%), or PDR (0.68%); after 10 years, the respective cumulative incidences were 16.4, 1.2, and 1.5%. Among those with nonproliferative (background) retinopathy at baseline, after 5 years 23% developed preproliferative retinopathy, 5.2% developed maculopathy, and 6.1% developed PDR; after 10 years, the respective cumulative incidences were 53%, 9.6%, and 11%. Patients with nonproliferative retinopathy at baseline were five times more likely to develop preproliferative, PDR, or maculopathy than those without retinopathy at baseline (adjusted hazard ratio 5.0 [95% CI 4.4–5.6]).

**CONCLUSIONS**—Few patients without diabetic retinopathy at the initial screening examination developed preproliferative retinopathy, PDR, or sight-threatening maculopathy after 5–10 years of follow-up. Screening intervals longer than a year may be appropriate for such patients.

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Regular retinal examination is a cornerstone of good diabetes care and is intended to diagnose diabetic retinopathy before it causes visual loss so that effective treatment can be given (1). In the U.K. and the U.S., annual screening has been recommended for all patients with diabetes—even in patients without diabetic retinopathy at earlier examinations (2,3). However, the frequency of retinal examination is a major determinant of the effectiveness and cost-effectiveness of

screening programs (4) and so should be based on accurate contemporary evidence of the rates at which retinopathy begins and progresses. In the U.K., retinopathy screening programs have grown in size and cost while yields have dropped, so it is timely to consider whether screening intervals should be increased for patients at low risk of progression (5).

Epidemiological studies have shown that major predictors of retinopathy progression are the presence and severity of

retinopathy at a patient's first retinal examination. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found that, of people with diabetes diagnosed at  $\geq 30$  years of age and without retinopathy at baseline, only 0.4% of noninsulin users and no insulin users progressed to proliferative diabetic retinopathy (PDR) over 4 years (6). In contrast, 9% of participants with early retinopathy at baseline progressed to PDR over 4 years. Since WESDR was conducted during the 1980s, there have been major changes internationally in the diagnosis and treatment of diabetes, in diabetic retinopathy, and in the prevalence and treatment of risk factors, so epidemiological evidence from previous decades may no longer be relevant. Large-scale and long-term screening programs can provide such evidence.

We previously reported on a cohort of 20,788 people in England mostly with type 2 diabetes and followed for up to 17 years in a community screening program for patients looked after in primary care (5). We found that screening intervals of between 18 and 24 months were not associated with higher prevalence of PDR at screening, compared with intervals of 12–18 months, but that intervals of over 24 months were. That study focused on prevalence of retinopathy at the time of screening but not on incidence or progression rates. The aims of the current study were to estimate retinopathy incidence and progression rates by longitudinal analysis of individual patient data from this cohort and to compare rates between those with different grades of or no retinopathy at their first retinal examination.

## RESEARCH DESIGN AND METHODS

The study had a dynamic cohort design, i.e., individuals entered or left the cohort at various times. The study population comprised all 20,686 people with diabetes screened by the Central Norfolk Diabetic Retinopathy Screening Service at any time between January 1990 and December 2006, after excluding 102

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patients who already had sight-threatening maculopathy or PDR at their first retinal examination. No sampling was used. All patients with type 2 diabetes, excluding those under the continuing care of an ophthalmologist or attending hospital diabetic clinics, were identified from diabetes registers kept by all general practices in Norfolk. In addition, 205 younger, probably type 1 diabetic, patients cared for by their general practitioners were also included. In the U.K., practically the entire population is registered with a local general practitioner. By the end of 2006, a total of 12,901 patients with diabetes and registered with their general practices were eligible and invited for screening, of whom 10,312 (80%) were screened within a year, indicating the program's coverage of the local population. Total numbers of patients eligible for screening in preceding years are unknown because until then each general practice, rather than the program administrators, held the lists of eligible patients.

### Screening procedures

Every year, registered patients with diabetes were invited to undergo retinal screening, which was carried out at their general practices with mobile retinal cameras operated by trained retinal screeners. All patients were invited for annual screening except those with more severe nonproliferative retinopathy, questionable images, or technical problems, who were rescreened after 6 months. During each screening episode, both pupils were dilated with 1% tropicamide drops. Two photographs of each eye were taken, one centered on the optic nerve and the other on the fovea, using Canon 45NM or 46NM fundus cameras (Canon UK, Reigate, U.K.) with 45° fields and Orion Eyecap and DRSS digital imaging software.

Before 2000, all images were captured on color transparency film and subsequently graded by a diabetologist with a specialist interest in retinopathy (R.H.G.). From 2000 onward, digital imaging was introduced and grading was carried out by a total of seven primary graders, four ophthalmologists, one diabetologist, one general practitioner, and one nationally accredited arbitration grader. From 1990 to 2002, a descriptive grading system based on European guidelines (7) was used. From 2003 onward, the virtually identical U.K. National Screening Committee grading system (8) was adopted. After 2006, a system of primary, secondary, and arbitration grading was set up as defined by the

English National Screening Program for diabetic eye disease. Both systems graded retinas as having no retinopathy, nonproliferative (background) retinopathy, preproliferative retinopathy, PDR, or sight-threatening maculopathy. These grades were roughly equivalent to, but simpler than, the Early Treatment Diabetic Retinopathy Study grading system (9). For this study, a patient's retinopathy grade was defined according to their worse eye.

If screening identified preproliferative retinopathy, PDR, or sight-threatening maculopathy, patients were referred to hospital eye services for further assessment, treatment if required, and follow-up. PDR or sight-threatening maculopathy that was considered to be sight-threatening retinopathy usually required laser photocoagulation to prevent progressive visual loss. Those with significant nondiabetic lesions such as cataracts were also referred to hospital eye services. While in the hospital eye service, patients were excluded from the screening program cohort.

### Statistical analysis

The statistical analyses aimed to estimate the cumulative incidence and annual incidence rates of different grades of retinopathy in relation to the findings of their first screening examination and other measured risk factors. Cumulative incidence rates were estimated with life tables. Annual incidence rates were estimated by dividing the numbers of incident cases by the respective person-years at risk. These incidence rates were by definition hazard rates because each individual's time at risk ended when the respective outcome was first detected and because the outcome could not recur. If the respective grade of retinopathy was never detected, each patient's follow-up was censored at the time of their latest screening examination. For life table analyses, censored observations were treated as if they were withdrawn halfway through the year. We also investigated relationships between the time taken to progress between retinopathy grades and patients' baseline grading and other prognostic characteristics. For this, Cox proportional hazards regression models were used, with baseline age, duration of diabetes, type of diabetes treatment, and hypertension treatment as prognostic variables. Details of other risk factors such as smoking history, blood glucose, glycated hemoglobin, blood pressure, sex, and ethnicity were not available to the screening program. For all longitudinal analyses, the

primary outcome was the time from the date of their first screening examination until the first time the respective grade of retinopathy was detected. Patients with proliferative retinopathy or sight-threatening maculopathy at baseline were excluded from all analyses. The study was approved by the East Norfolk and Waveney Research Ethics Committee.

**RESULTS**—Of 20,686 patients without PDR or maculopathy at baseline, 16,444 (79.5%) had no retinopathy, 3,632 (17.5%) had nonproliferative retinopathy, and 610 (3.0%) had preproliferative retinopathy. Table 1 shows the baseline characteristics of patients in relation to the findings of their first screening examination. More severe retinopathy was associated with longer duration of diabetes and treatment with insulin and was inversely associated with dietary treatment only. Although age and hypertension treatment differed significantly between these groups, there were no clear trends with increasing severity of retinopathy. Those with retinopathy at baseline subsequently tended to have shorter follow-up and fewer screening examinations over time than those without retinopathy at baseline because referral to the hospital eye service removed them from the screening cohort. Of 42,843 screening examinations carried out after each patient's baseline examination, the screening interval since the previous examination was <12 months in 7%, 12–18 months in 49%, between 18 and 24 months in 23%, and >24 months in 21%.

Among patients without retinopathy at baseline, after 5 years of follow-up their cumulative incidence of nonproliferative retinopathy was 36%, preproliferative retinopathy 4.0%, maculopathy 0.59%, and PDR 0.68%. After 10 years of follow-up, the respective cumulative incidences were 66, 16, 1.2, and 1.5%. Complete life tables with numbers of patients at risk and developing retinopathy for each year of follow-up—i.e., for up to 17 years—are shown in Supplementary Data Table A. A total of 83 of these patients developed sight-threatening maculopathy, and 67 developed PDR.

Among patients with nonproliferative retinopathy at baseline, after 5 years of follow-up their cumulative incidence of preproliferative retinopathy was 23%, maculopathy 5.2%, and PDR 6.1%. After 10 years of follow-up, the respective cumulative incidences were 53, 9.6, and 11%. Complete life tables for up to 17 years of

Table 1—Characteristics of patients without PDR or maculopathy at baseline and characteristics of their screening

	No retinopathy	Nonproliferative retinopathy	PDR	p*
n	16,444	3,632	610	
Age (years)#	66.7 (58.0–74.5)	68.0 (58.5–75.7)	66.3 (55.7–66.3)	0.005
Diabetes duration (years)#	1 (0–3)	2 (1–6)	3 (1–10)	<0.001
Age at diagnosis (years)#	63.9 (55.1–71.9)	63.6 (53.7–72.0)	60.0 (48.5–69.3)	<0.001
Follow-up duration (years)**	2.5 (0–5.5)	1.4 (0–4.0)	0 (0–2)	<0.001
No. of screening visits**	3 (1–10)##	2 (1–10)##	1 (1–7)##	<0.001
Diabetes treatment at baseline#				<0.001
Diet only	4,006 (24.4)	733 (20.6)	76 (13.3)	
Oral hypoglycemics only	1,1631 (70.8)	2,510 (70.4)	415 (72.6)	
Insulin	787 (4.8)	324 (9.1)	81 (14.2)	
Hypertension treatment#	10,313 (62.7)	2,111 (59.1)	349 (61.0)	<0.001

Data are median (interquartile range) or n (%) unless otherwise indicated. \* $\chi^2$  test for categorical variables and Cuzick nonparametric test for trend for continuous variables. #Baseline characteristics. \*\*Screening characteristics. ##Range.

follow-up are shown in Supplementary Data Table B. A total of 84 of these patients developed sight-threatening maculopathy, and 99 developed PDR. The incidence rates of retinopathy progression according to

baseline retinopathy grade are shown in Fig. 1, Supplementary Table C, and Supplementary Fig. A.

The hazard of developing preproliferative retinopathy, PDR, or maculopathy,

among patients without these grades at baseline, was five times higher in those with nonproliferative retinopathy at baseline than in those without retinopathy at baseline after adjustment for age, duration and treatment of diabetes, and hypertension treatment in a Cox regression analysis model (Table 2).

The hazard of maculopathy or PDR, among patients without these grades at baseline, was almost ten times as high in those with preproliferative retinopathy at baseline (adjusted hazard ratio 9.9 [95% CI 5.1–19.2]), and over seven times as high in those with nonproliferative retinopathy at baseline (7.5 [5.5–10.1]) compared with patients without retinopathy at baseline after adjustment for other risk factors in a Cox regression analysis model (Supplementary Data Table D).

Figure 1 shows that the incidence rate of preproliferative retinopathy, PDR, or maculopathy—i.e., referable disease—during 12 years of follow-up tended to increase over time up to 18% per year in those with nonproliferative retinopathy at baseline; the incidence rate remained <10% per year in those without retinopathy at baseline. Supplementary Data Fig. A shows that the incidence rate of maculopathy or PDR, i.e., treatable disease detected by screening, increased to 35% per year after 5 years' follow-up in those with preproliferative retinopathy at baseline, varied between 0 and 2% per year in those with nonproliferative retinopathy at baseline, and remained <0.5% per year for those without retinopathy at baseline. In both figures, the truncated lines and widening CIs with longer follow-up are due to smaller numbers of patients and shorter time at risk among those with retinopathy at baseline.

**CONCLUSIONS**—The study shows that people with type 2 diabetes without retinopathy at the time of their first retinal examination were at low risk of progressing to preproliferative retinopathy (requiring referral to an ophthalmologist) and at very low risk of progressing to either PDR or maculopathy (requiring treatment) even after 5 years of follow-up. In contrast, patients with nonproliferative or preproliferative retinopathy at their first retinal examination were at much higher risk of progression. These findings support increasing the screening intervals in people with diabetes and without retinopathy detected at earlier screening examinations and are in keeping with our previous analysis of retinopathy prevalence

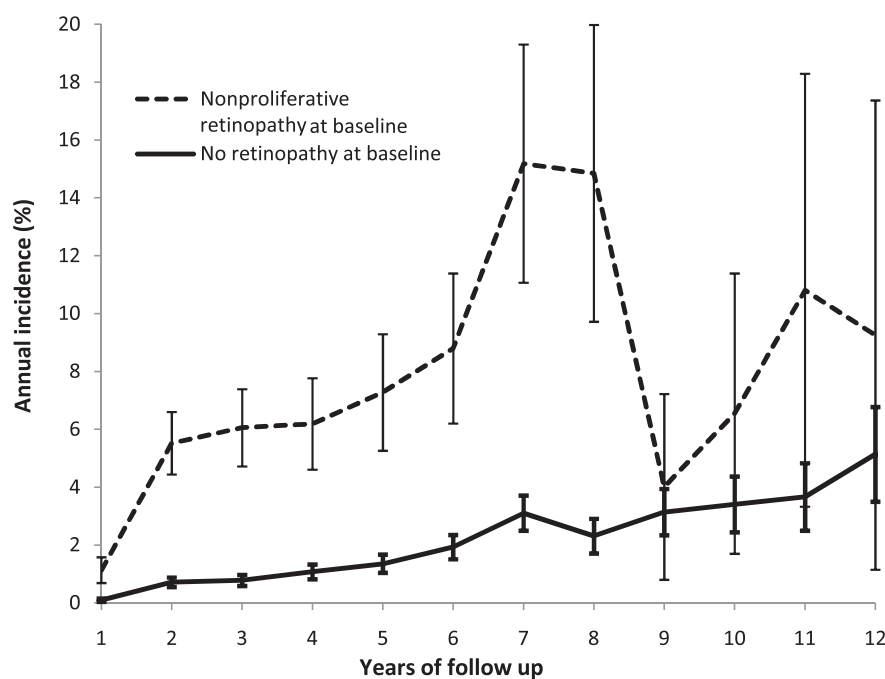


Figure 1—Annual incidence, with 95% CIs, of preproliferative retinopathy, PDR, or maculopathy in patients with nonproliferative retinopathy or without retinopathy at baseline. Follow-up truncated after 12 years because of small numbers (<24 incident cases per year).

**Table 2—Relationship between baseline characteristics and time to preproliferative retinopathy, PDR, or maculopathy (1,264 cases) among patients with nonproliferative retinopathy or without retinopathy at baseline: Cox regression analysis model**

Baseline characteristic	Adjusted hazard ratio	95% CI
Nonproliferative retinopathy at baseline		
No	1	—
Yes	4.97	4.41–5.60
Age (years)		
<40	1.49	1.09–2.05
40 to <70	1	—
≥70	1.26	1.00–1.27
Years since diabetes diagnosis		
<10	1	—
10 to <20	1.21	1.01–1.44
≥20	0.93	0.68–1.26
Diabetes treatment at baseline		
Diet only	1	—
Oral hypoglycemics only	1.77	1.44–2.17
Insulin	2.17	1.68–2.81
Hypertension treatment		
No	1	—
Yes	0.72	0.64–0.81

at screening (5) and with other longitudinal studies of retinopathy incidence and progression (6,10–13). In this program, 80% of patients had no retinopathy at their first examination, so screening them less frequently could substantially reduce costs, allow limited resources to be shifted to higher-risk patients, and thus increase cost-effectiveness of screening overall.

The most comparable longitudinal studies of retinopathy progression among patients with predominantly type 2 diabetes are the WESDR (6,10) and the Liverpool cohort study (11). As mentioned earlier, WESDR found a low incidence of PDR in patients without retinopathy at baseline. The more recent Liverpool cohort study followed 4,770 patients newly diagnosed with type 2 diabetes for up to 6 years and found that the annual incidence of sight-threatening maculopathy or retinopathy increased from 0.31% during the first year to 1.8% during the sixth year, and the cumulative incidence after 6 years was 6.1% (11). In those with preproliferative retinopathy at baseline, the cumulative incidence of sight-threatening maculopathy or retinopathy after 6 years was 70%. In the UK Prospective Diabetes Study of 2,316 patients with type 2 diabetes and without retinopathy at baseline, 0.2% needed photocoagulation at 3 years, 1.1% at 6 years, and 2.6% at 9 years (12,13). Among 509 patients with any retinopathy at baseline, 15% required

photocoagulation by 3 years and 32% by 9 years. A much smaller study that over 4 years followed a cohort of 120 patients with type 2 diabetes and without retinopathy at their first screening found that only 5% developed mild retinopathy by year 1 and that one patient developed moderate retinopathy. By year 2, an additional 23 patients had developed some retinopathy but only 1 of these was classified as having severe nonproliferative retinopathy, while by year 4 nearly half of the patients had developed some retinopathy and only 1 patient had developed proliferative retinopathy (14). These studies all suggest that screening could be done less frequently in patients without retinopathy at their first examination than in those with retinopathy.

Our findings are not directly comparable with these longitudinal studies owing to slightly different definitions of retinopathy, durations of follow-up, and statistical methods. However, our estimates of the incidence of PDR or maculopathy are similar to those in WESDR but lower than those in Liverpool. Our low rates of PDR or maculopathy may be partly attributable to this program's referral of patients to specialist services at an earlier stage of progression, despite the statistical censorship and multivariable adjustment. This meant that the highest-risk patients were selectively removed from this screening cohort after detection of preproliferative retinopathy.

The result most relevant to the design of screening programs, however, is the incidence of preproliferative retinopathy, which in the U.K. is the diagnostic threshold for referral to specialist eye care. Our cumulative incidence of preproliferative retinopathy in those without retinopathy at baseline was 6.8% after 6 years, which was similar to the 7.1% found in Liverpool (11). Our cumulative incidence of preproliferative retinopathy in those with nonproliferative retinopathy at baseline was 29%, which was also similar to the 33% found in Liverpool. Thus, our incidence estimates for preproliferative retinopathy are probably robust, and our incidence estimates for maculopathy and PDR are probably biased downward.

Our Cox regression analysis showed that age, duration of diabetes, and treatment of diabetes and hypertension were independent risk factors for retinopathy progression, in keeping with previous studies (6,10,13) and with our analysis of prevalent retinopathy in this cohort (5). These findings are a reminder that risk factors other than presence of retinopathy should also be considered if screening intervals are varied according to patients' risk profiles. Screening protocols should therefore also take account of other risk factors such as diabetes duration and treatment and metabolic control, blood pressure, lipid levels, and age.

The main strength of the study was the large size of the cohort and the long duration of follow-up, both of which greatly exceed any of the other studies cited. The study was original in combining life table analysis to estimate incidence rates for retinopathy progression, with multivariable survival analysis to quantify the independent effects of several risk factors. Previous studies have used either method but not both. The main limitations were the lack of data on progression after referral to the hospital and the lack of information on patients' glucose and glycated hemoglobin levels, blood pressure, smoking history, and other microvascular risk factors. The tendency of screening intervals to increase with increasing duration of follow-up (Spearman rank correlation test,  $P < 0.001$ ) could partly account for the increasing annual incidence of retinopathy seen with increasing duration of follow-up. Finally, the study outcomes—presence and grade of retinopathy—were defined by screening program graders using retinal photographs rather than by ophthalmologists using slit lamps, which are considered to

be the definitive diagnostic method. However, our grading of retinal photographs was subject to standardized training and quality-assurance procedures.

In summary, this study provides further evidence in support of increasing diabetic retinopathy screening intervals to more than a year in patients without retinopathy at the time of their first retinal examination. These findings should be evaluated with a randomized trial.

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C.D.J. researched data and wrote the manuscript. A.M. researched data and reviewed and edited the manuscript. R.H.G. researched data and reviewed and edited the manuscript. M.O.B. researched data and wrote the manuscript. M.O.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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