Objective: To examine the outcome of digital epiluminescence microscopic (DELM) surveillance of atypical nevi in a high-risk population for 4 years.

Design: Atypical, flat melanocytic lesions in 100 patients at high risk of developing melanoma were followed annually with DELM. Pigmentary changes or an increase in DELM diameter of 1 mm or greater was an indication to perform an excisional biopsy.

Setting: Cardinal Bernardin Cancer Center Melanoma Program, Loyola University Health System, Maywood.

Patients: A consecutive sample of 3482 lesions from 100 patients (aged 18-65 years) with at least 2 images of the same lesion.

Main Outcome Measures: The DELM change was confirmed by histopathologic examination. Patient confidence in and comfort with dermatologic surveillance and skin self-examination performance were assessed.

Results: During annual surveillance with DELM, 5.5% of the lesions changed. Among the 193 excisional biopsy specimens there were 4 melanomas in situ, 169 dysplastic nevi, and 20 common nevi. Confidence in and comfort with surveillance and skin self-examination improved after DELM.

Conclusions: The criteria applied to detect substantial DELM changes were an increase in DELM diameter of 1 mm or greater and pigmentary changes, including radial streaming, local enlargement, peripheral black dots, and “clumping” within the irregular pigment network. Use of DELM enhanced confidence in and comfort with care, which extended to performing more extensive skin self-examination.

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ALTHOUGH EXPERIENCED dermatologists diagnose most melanomas with the unaided eye, epiluminescence microscopy (ELM) enhances the diagnostic accuracy of early cases and helps select pigmented lesions that require biopsy.1-2 Most dermatologists agree that patients with atypical or dysplastic nevi are at increased risk of developing melanoma,6 and they follow up patients with total cutaneous examination either annually or every 4 to 6 months. Since dysplastic nevi either are precursors to melanoma7-13 or identify persons at risk of developing melanoma,14-16 intense surveillance of atypical nevi and new pigmented lesions is performed so that melanomas can be found and removed in the early curable phase. For people with dysplastic nevi, the risk of developing melanoma increases with a personal history of melanoma, and each first-degree relative with melanoma confers risk (eg, 1 first-degree relative: relative risk = 4).15,17

Dermatologists use total cutaneous photographs to monitor patients for new lesions and changes in atypical nevi.1,18 Digital ELM (DELM) (digital dermoscopy), which archives images of nevi, supports surveillance of atypical nevi with 30-fold magnification of pigmentary structural components.19,20 Digital ELM assists in short-term digital monitoring of suspicious nevi (which are followed for 3 months, and those with changes are excised21) and long-term surveillance of nevi.22-26 We report our experience with a population with multiple atypical nevi followed annually with DELM using defined criteria of change for biopsy of nevi.

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METHODS

GENERAL CHARACTERISTICS OF THE POPULATION

Between January 1, 1998, and December 31, 2002, 100 patients underwent baseline DELM and annual imaging of atypical nevi. A derma-
tologist (J.K.R.) evaluated the patients clinically 6 months after DELM imaging sessions. Clinical inclusion criteria for DELM were 50 or more melanocytic nevi27 with at least 1 nevus measuring 8 mm or more in diameter, a personal or family history of a melanoma in a first- or second-degree relative, and at least 3 clinically atypical nevi with 3 of the ABCD criteria found in melanoma: asymmetry, color variation over the surface of the nevus (irregular pigmentation), and hazy or irregular borders.29 The patients were at least 18 years old when baseline DELM was performed. The pathology reports of nevi and melanomas removed before entry into the study were reviewed. The pathological specimens of those with a history of melanoma were reviewed. Patients entered into the study had at least 3 mild, moderate, or severely dysplastic melanocytic nevi with architectural disorder.29,30 The numbers and locations of dysplastic nevi, melanomas in situ, and invasive melanomas were recorded.

Patients were informed of their increased risk of developing melanoma and that they could develop new melanocytic nevi throughout their lives. During the initial DELM session, aspects of the lesions with the ABCD criteria were demonstrated using their DELM images. Patients were encouraged to perform monthly skin self-examination (SSE) and to compare their nevi with baseline photographs when they were available.

DELM TECHNIQUE

The total-body and individual images of patients’ multiple clinically atypical nevi and common nevi were examined and electronically stored using a DELM imaging system (MoleMax II, Derma Instruments, Vienna, Austria). The system offers a maximum field of view of 1 cm with 30-fold magnification. Melanocytic skin lesions with a maximum diameter exceeding the field of view of the electronic camera were not included in this study. Digital ELM images were stored without compression in bitmap format. The pixel resolution of each image was 640 × 480 at 24-bit color depth.

For atypical flat or only slightly raised nevi without a history of change or surface microscopic evidence of melanoma with a diameter of 3 mm to 1 cm, the entire surface was encompassed by the DELM system. Nevi on contoured surfaces, for example, the ear, were compressed with the DELM unit. If it was not possible to adequately flatten the area, the image was not obtained. Lesions meeting melanoma-specific criteria were not entered into the study to be followed for change over time because they were surgically removed before entry into the study. Atypical nevi had 1 or 2 of the following ELM features described by Kittler et al23,24: an irregular or nonuniform pigmentation network, irregular overall pigmentation, asymmetry of color or contour along 1 axis, central black dots, radial streaming, and scarlike depigmentation.26-28 All clinically atypical nevi 3 mm or more in diameter and selected common nevi greater than 5 mm in diameter were electronically archived. One dermatologist (J.K.R.) examined all patients and imaged nevi with a low level of clinical suspicion; therefore, biopsy was not performed at the first visit.

At the annual examination, nevi were examined by DELM and the images were stored. New nevi greater than 3 mm in diameter were added to the patient’s total images. The dermatologist performed online side-by-side comparison of DELM images at each follow-up visit of the respective patient for each lesion on file and made clinical decisions about performing a biopsy.

EXCISIONAL BIOPSY

Criteria for excisional biopsy of nevi followed by DELM were morphologic changes of regression, color change with the appearance of new colors, enlargement along 1 axis causing asymmetry of the shape of the lesion, asymmetry of the pigmenitary pattern, and the appearance of structural ELM changes such as irregularly distributed black dots in the periphery, radial streaming, whitish veil, gray-blue area, pseudopods, the appearance of “clumping” or broadening of the prominent irregular or nonuniform pigment network, and a change in the scarlike depigmentation.23,24 The criteria used for excisional biopsy are those of Kittler et al,23 with the addition of clumping or broadening of the prominent irregular pigment network and an increase of 1 mm or more in DELM diameter compared with previous images.

Since the pressure of applying the instrument to the skin may produce minor variations in diameter, symmetrical enlargement less than 1 mm was not a criterion for biopsy. When the nevus was located in an anatomic area undergoing a rapid increase in size, for example, the abdomen in pregnant women, an increasing diameter was not sufficient to warrant biopsy. Overall pigmentation change in many nevi consistent with pigmenitary change in the surrounding skin from seasonal solar exposure was not an indication to perform a biopsy. A decrease in brown globules and disappearance of black dots were not changes that prompted biopsy of the lesion.

Standard histologic examination of serial step sections was performed on all excised lesions. The histopathologic diagnosis of dysplastic nevi and early melanoma was based on established architectural and cellular criteria.29,30

CONFIDENCE IN AND COMFORT WITH SURVEILLANCE METHODS

Before and after the first year of DELM surveillance, patients completed a brief survey using a 5-point scale to define their confidence in the dermatologist and their comfort with being monitored by visual examination, photographic comparison, and DELM. Additional questions used a 5-point scale to define their confidence in and comfort with performing monthly SSE and performance of SSE before and after having DELM and using photographs for SSE. Patients provided their opinion of the advantages and disadvantages of DELM. Data are given as mean (SD) unless otherwise specified.

RESULTS

GENERAL CHARACTERISTICS

The study population of 100 patients (mean age, 38.4 years; 72% women) included 81 with a personal history of melanoma in situ or invasive melanoma (Table 1). During the 4-year period, 1532 melanocytic skin lesions had at least 3 sequentially recorded images and 1950 had 2 recorded images by DELM. At the annual follow-up examination, 215 new nevi greater than 3 mm in diameter were added to the patients’ total images and have only 1 recorded image. Thus, during the 4-year period, a total sample of 3697 nevi had images stored, with 3482 having 2 or more images. Nevi were compared with baseline images in side-by-side comparison and stored in years 1 and 2. If there was no change in the nevus in study years 3 and 4, then the image was not stored. The median number of lesions evaluated and stored sequentially for 3 or more years was 15 per patient (range, 2-35). The median total follow-up interval was 36.2 months (range, 12-48 months). Eighty percent of all follow-up intervals ranged from 24 to 36 months.
PATHOLOGY OF ELM FEATURES

In the 4 years of surveillance, 193 excisional biopsies were performed in 55 patients (mean age, 32.8 years; 60% women) (Table 2). The pathological findings showed no invasive melanomas, 4 melanomas in situ in 4 individuals, 169 dysplastic nevi in 37 individuals, and 20 benign nevi in 14 individuals (Table 2) (Figures 1, 2, and 3). Median follow-up for excised lesions was 12.3 months (range, 3.0-32.5 months).

One of the discriminatory features of melanoma, radial streaming, was found in a melanoma in situ that changed in 1 year (Figure 1). This case also illustrates clumping or broadening of the prominent irregular or nonuniform pigment network seen in the initial lesion. This clumping of the prominent irregular pigment network was noted in another melanoma in situ. The intraepidermal nests of severely atypical melanocytes seen in the serial section (Figure 1D) correspond to the radial streaming at the 6-o'clock position of the DELM image of the lesion (Figure 1C) and of the specimen, which was grossed and inked to orient the 6-o'clock margin.

Another significant pigmentary feature of melanoma is peripheral black dots. One patient had a single black dot appear at the periphery of the atypical nevus (Figure 2C, black dot at 2 o’clock). The pathological section through the black dot shows nests of cells with moderate atypia at the tips of the rete ridges (Figure 2F). During the first trimester of pregnancy (14 months after baseline imaging), focal enlargement developed in 1 dimension (change in shape), and the irregular pigment network became more prominent. Although this case has a more prominent irregular pigment network, it does not have the dense central clumped pigmentation seen in the DELM of melanoma in situ of the case shown in Figure 1. The clinical photograph of the lesion shows a single darker area consistent with the peripheral black dot and the irregular pigment network.

The final significant DELM feature, focal enlargement, can be seen in atypical nevi and melanoma. In the case of a mildly dysplastic compound nevus, there was focal enlargement in 1 dimension 1 year after the initial image was acquired (Figure 3B).

During this study, 3482 nevi were monitored for at least 12 months, and 193 underwent biopsy for change. Thus, 5.5% of the pigmented lesions demonstrated changes on DELM and were excised. There were no significant differences in the rate of biopsy among the 3 categories of risk: personal history of melanoma (median, 2.0; range, 0-5), family history of melanoma in 1 first-degree relative (median, 2.0; range, 0-6), and family history of melanoma in 2 or more first-degree relatives (median, 1.0; range, 0-2) (Kruskal-Wallis test, P=.20) (Table 2).

The median diameter of the excised lesions was 4.3 mm (range, 3.3-6.2 mm). There is a significant difference in the diameter of the 3 types of excised pigmented lesions (Kruskal-Wallis test, P<.001) (Table 2). Biopsies are performed of melanomas in situ and dysplastic nevi with smaller diameters than those of common nevi (Wilcoxon signed rank test, P<.001).

| Table 1. Characteristics of 100 Patients at High Risk of Developing Melanoma |
|---------------------------------|--------------|--------------|
| Characteristic                  | Patients, No. |              |
|                                 | Women        | Men          |
| ≥3 Pathologically dysplastic nevi and ≥50 nevi                       | 72           | 28           |
| Personal history of melanoma               |              |              |
| Melanoma in situ                              | 21           | 2            |
| Melanoma ≤1.0 mm                              | 35           | 19           |
| Melanoma >1.0 mm                              | 0            | 4            |
| Total                                       | 56           | 25           |
| or Family history of melanoma in 1 first-degree relative                  | 12           | 3            |
| Family history of melanoma in ≥2 first-degree relatives                  | 4            | 0            |

Focal or symmetrical enlargement occurred in 95% of the dysplastic nevi and in 100% of the melanomas in situ (Table 3). Change is symmetrical when the lesion enlarges symmetrically even if the lesion was asymmetrical at the time of presentation. Pigmentary structural features associated with melanoma in situ are radial streaming, pseudopods (focal enlargement), peripheral black dots, and clumping within the irregular pigment network. Regression was not seen in any of the lesions followed in this study. The remaining melanocytic lesions (87.4%) were stable over time or had overall darker or lighter appearance associated with pigmentary change in the surrounding skin.

CONFIDENCE IN AND COMFORT WITH SURVEILLANCE METHODS AND PERFORMANCE OF SSE

Patients had a greater degree of confidence in and more comfort with their surveillance by DELM than with visual examination or photographs before DELM (paired samples test, P<.001) (Table 4). Confidence in and comfort with performing SSE improved after DELM for those using visual SSE and those with photographs. Those with photographs practiced the most extensive SSE after DELM (Table 5). The advantages of DELM were fewer scars from biopsies and peace of mind; the disadvantage was the amount of time it took to perform DELM.

Patients with multiple atypical nevi may have many, sometimes hundreds, of clinically abnormal–appearing nevi. Surveillance of these nevi is complicated by the multiplicity of atypical nevi. The differentiation of atypical nevi from early melanomas is especially challenging for small-diameter lesions (3-6 mm in diameter). This study of 100 individuals demonstrates a 5.5% rate of change in the 3482 nevi followed annually. In a study of a European population by Kittler et al., 74% (4%) of 1862 sequentially recorded nevi demonstrated changes requiring biopsy. Despite different populations and slightly different entry criteria, the 2 studies dem-

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onstrate almost the same ratio of change in nevi. Because 81% of the individuals entered into this study had a history of melanoma in situ or invasive melanoma, we chose to monitor many common junctional nevi with DELM to try to assure the patient that early melanoma would not be overlooked.

The changes in nevi that prompted biopsy were an increase in DELM diameter of 1 mm or more in 1 axis and changes in the ELM pigmentary patterns, with the appearance of radial streaming, clumping or broadening of the irregular pigment network, peripheral black dots, and local enlargement in 1 dimension. The histo-

Table 2. Histologic Diagnosis in 193 Biopsy Specimens From Changing Pigmented Lesions

<table>
<thead>
<tr>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>$\geq 3$ Histologically dysplastic nevi and $\geq 50$ nevi (n = 100) and</td>
<td>193</td>
<td>4</td>
<td>169</td>
<td>20</td>
</tr>
<tr>
<td>Personal history of melanoma in situ or invasive melanoma (n = 81) or</td>
<td>155</td>
<td>1</td>
<td>142</td>
<td>12</td>
</tr>
<tr>
<td>Family history of melanoma in 1 first-degree relative (n = 15)</td>
<td>34</td>
<td>1</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Family history of melanoma in $\geq 2$ first-degree relatives (n = 4)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diameter, median (range), mm (single greatest dimension)</td>
<td>4.3 (3.3-6.2)</td>
<td>4.2 (3.8-4.6)*</td>
<td>4.3 (3.3-6.5)*</td>
<td>5.1 (4.1-6.2)*</td>
</tr>
</tbody>
</table>

*The difference in the diameter of the excised pigmented lesions is significant (Kruskal-Wallis test, $P < .001$). Melanomas in situ and dysplastic nevi undergo biopsy with smaller diameters than common nevi (Wilcoxon signed rank test, $P < .001$).
pathologic correlate of radial streaming is a discrete linear array of junctional nests of atypical melanocytes at the periphery of the lesion, as observed in the case of melanoma in situ (Figure 1F). The clinical correlation of radial streaming and pseudopods is an irregular border (Figure 1D). Although no single criterion is 100% diagnostic of melanoma, radial streaming, clumping or broadening of the irregular pigment network, and peripheral black dots may be discriminating features for early melanoma. Although the diagnostic sensitivity of ELM
ranges from 88% to 95% in various studies, false-negative diagnosis by dermatoscopy is not theoretical; 4 of 55 melanomas in a recent study were missed by DELM.

Because of the consequences of a false-negative diagnosis, the DELM criteria for excisional biopsy in this high-risk population were conservatively defined as fo-

**Figure 3.** A, Baseline digital epiluminescence microscopic (DELM) image showing an atypical nevus of the toe. B, One-year DELM image showing focal enlargement in 1 dimension (change in shape) (magnification of parts A and B is identical [original magnification ×30]). C and D, The superior area of focal growth shows a mildly dysplastic compound melanocytic nevus with prominent bridging of rete ridges and slight cytologic atypia (hematoxylin-eosin, original magnification ×20 and ×200, respectively).

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**Table 3. Frequency of Change in Size and Pigmentation by Histologic Diagnosis**

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>Change in Size, No.</th>
<th>Pigmentary Structural Changes, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symmetrical Enlargement</td>
<td>Focal Enlargement (Asymmetrical Shape)</td>
</tr>
<tr>
<td>Common nevi (n = 20)</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Dysplastic nevi (n = 169)</td>
<td>26</td>
<td>135</td>
</tr>
<tr>
<td>Melanomas in situ (n = 4)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*More than 1 feature may change in a single pigmented lesion. Regression was not noted in any lesions in this study.
cal change in size of DELM diameter of 1 mm or greater in any axis or DELM pigmented change, including radial streaming, peripheral black dots, pseudopods, and prominent clumping of the irregular pigment network. Similarly, in this study of a high-risk population, small, clinically atypical nevi at least 3 mm in diameter were imaged to reduce the risk of missing small-diameter lesions at the time of clinical examination and failing to record them with DELM. Given the increased risk of developing melanoma in patients in this study, we performed a biopsy on all nevi with changes detected by DELM. Since 31% to 69% of common nevi also change, the excised lesions included common nevi as well as dysplastic nevi and melanomas in situ. Melanomas in situ and dysplastic nevi that underwent biopsy in this study had a smaller median diameter than common nevi. Because DELM detects changes in small-diameter melanomas in situ before they become invasive, observation of clinically atypical nevi becomes feasible and reassuring to those with the certain knowledge that they will develop more melanomas. Detection at this point also results in less scarring than is caused by wide local excision of invasive melanoma (Figure 2A).

Surveillance with DELM can reduce the cost of caring for patients with multiple atypical nevi compared with excision of all their nevi and spares patients the potentially painful and unsightly scars from multiple biopsies. High-risk patients with periodic surveillance tend to have significantly thinner, less invasive melanomas and small-diameter lesions compared with those whose tumors are self-diagnosed. Changes in small-diameter tumors might be overlooked in the absence of archival images. The surveillance interval commonly accepted by dermatologists is annually or every 4 to 6 months. The intervals are supported by case reports of patients followed by DELM. In this study, 4 cases of melanoma in situ were detected during annual DELM. The surveillance interval is also affected by patient comfort and SSE performance with detection of suspicious lesions. Patient satisfaction with and confidence in care may be attributed to the interpersonal skills of the physician and the health care team in addition to the technology.

In this study, melanomas in situ with a median diameter of 4.2 mm were detected. The smaller diameter of melanoma in situ is consistent with the 6-mm diameter used in the ABCD rule for visual examination of invasive melanoma for lesions that have a period of horizontal growth along the epidermal-dermal junction before invading the dermis. Since 3 of the 4 melanomas in situ in this study demonstrated ELM features of melanoma, it may be possible to replace the time-consuming methods used in this study with dermatoscopy, whose use would be extended to include lesions of 3 mm or more in diameter.

Given the societal cost of advanced melanoma and the suffering of individuals and their families, physician surveillance of those at risk of developing melanoma is important, but the methods used need to be feasible. Clinical examination with a handheld dermatoscope by a dermatologist is readily performed. Total-body photographs used by the dermatologist and the patient for archival purposes may be supplemented with DELM of

<table>
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<th>Variable</th>
<th>No SSE, %</th>
<th>Face Only, %</th>
<th>Face and Body, %</th>
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</thead>
<tbody>
<tr>
<td>SSE before DELM; visual examination by dermatologist (n = 43)</td>
<td>60*</td>
<td>35*</td>
<td>5*</td>
</tr>
<tr>
<td>SSE after DELM; visual examination by dermatologist (n = 43)</td>
<td>25</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>SSE before DELM; photographs held by patient (n = 57)</td>
<td>42*</td>
<td>5*</td>
<td>53*</td>
</tr>
<tr>
<td>SSE after DELM; photographs held by patient (n = 57)</td>
<td>12</td>
<td>18</td>
<td>70</td>
</tr>
</tbody>
</table>

Abbreviations: DELM, digital epiluminescence microscopy; SSE, skin self-examination.

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