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Variability in Short-Wavelength Automated Perimetry Among Peri- or Postmenopausal Women: A Dependence on Phyto-Oestrogen Consumption?

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Variability in short-wavelength automated perimetry among peri- or postmenopausal women: a dependence on phyto-oestrogen consumption?

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ABSTRACT.

Purpose: **To determine whether the hill of vision for Short-Wavelength Automated Perimetry (SWAP) is shallower for women who consume phyto-oestrogen-rich foods than for women who do not.**

Methods: **Visual field data were compared for two groups of healthy amenorrhoeic women 48–69 years-old with normal vision and not using hormone replacement: (1) 24 subjects who reported consuming soy and/or flax products and (2) 20 subjects who reported not consuming these products. Two types of 24-2 visual fields were measured: (1) Full Threshold SWAP and (2) a white-on-white (W/W) field obtained using a Swedish Interactive Threshold Algorithm (SITA Standard).**

Results: **The reduction of SWAP sensitivity from the centre of the field (4 loci, mean eccentricity = 4.2°) to the periphery (20 loci, mean eccentricity = 21.9°) was less for soy/flax consumers than for nonconsumers, both with age-referencing (mean difference = 1.7 dB, $p = 0.018$) and without ($p = 0.012$). Corresponding distinctions existed for the SWAP – W/W difference, and there was minimal effect for W/W fields alone. The peripheral age-referenced SWAP sensitivities averaged 2.5 dB higher for consumers than nonconsumers ($p = 0.022$).**

Conclusion: **The between-group distinctions are consistent with the possibility (derived from the women's health literature) that phyto-oestrogens may counteract a decline of short-wavelength-sensitive cone-mediated response among postmenopausal women. These results suggest another potential application for SWAP outside its original intended purpose as a glaucoma test. Future studies should assess whether phyto-oestrogen consumption is most beneficial for women who are sufficiently young and/or not too far beyond menopause.**

Key words: ageing – blue cone – oestrogen – peripheral vision – visual field

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Introduction

The development of Short-Wavelength Automated Perimetry (SWAP) in the 1990s was intended to provide a practical means for detecting glaucomatous visual field loss at a relatively early time and for monitoring progression (or lack thereof) during a disease stage when white-on-white (W/W) static automated thresholds are affected little or not at all (Johnson et al. 1993). The scientific rationale for a test with these desired attributes reflected the well-founded assumption that stimulus conditions could be arranged to reduce functional redundancy, thereby revealing responses from a minimal number of visual pathways – perhaps even a single pathway – susceptible or vulnerable to the effects of glaucoma (Johnson 1994). It was reasonable to expect that this could be accomplished by assessing visual response mediated via short-wavelength-sensitive (SWS) cones (Sample et al. 1996) which signal to the cortex mainly via a limited number of specialized neurons (Solomon & Lennie 2007). However, it now appears that SWAP is not significantly better than W/W perimetry for detecting glaucoma (Bengtsson & Heijl 2006). This is due at least partly to the relatively high degree of variability inherent in SWAP sensitivity

measures, particularly when compared with sensitivity measures obtained using more standard W/W perimetry (Kwon et al. 1998; Blumenthal et al. 2003; Bengtsson et al. 2008). The analyses for the present study provide an initial assessment of a possible dietary source for some of this extra variability. In the process, these analyses point the way to a potential new application for SWAP, bearing on the substantial contemporary interest concerning the purported ability of oestrogenic change or oestrogenic agents to affect central nervous system (CNS) function, particularly after menopause (Morrison et al. 2006; Sherwin & Henry 2008).

The extra variability in SWAP is known to arise from multiple sources, some of which are universally appreciated [e.g. concerning lens density (Sample et al. 1994)] and some of which are not but have been forecast and documented nevertheless [e.g. concerning aspects of visual adaptation (Eisner et al. 2006b; Felius & Swanson 2003)]. It has come as more of a surprise that changes in hormone levels or hormonal function may affect SWS-cone-mediated response, at least for some women (Eisner et al. 2004a,b; Akar et al. 2005; Eisner & Incognito 2006; Verit et al. 2007; Eisner & Toomey 2008). In particular, increased oestrogen levels can lead to higher SWS-cone-mediated sensitivities (Eisner et al. 2004b; Akar et al. 2005).

To counteract the profound reduction in oestrogen synthesis occurring at the menopausal transition (Chahal & Drake 2007), many women have used hormone replacement. However, some women aim to counteract their oestrogen loss naturally by consuming foods rich in phyto-oestrogens (Fitzpatrick 2003), especially now that the publication of results from several clinical trials has generated skepticism about the use of medical or synthetic hormone replacement (Hoffmann et al. 2005; Serock et al. 2008). Thus, if changes in oestrogen activity are able to affect SWS-cone-mediated response, then to the extent that phyto-oestrogens are able to mimic effects of oestrogens (Cui et al. 2007; Turner et al. 2007; Occhiuto et al. 2008), perhaps they can affect SWS-cone-mediated response. In particular, the SWAP visual fields of women who consume phyto-oestrogen-rich foods may differ characteristically from the SWAP visual fields of women who do not. More specifically, because increased oestrogen levels may be associated with higher SWAP sensitivities overall (Akar et al. 2005), if there were an effect of phyto-oestrogens on the steepness of the hill of vision, the expectation would be that the fall-off of SWAP sensitivity from the centre to the periphery of the visual field would be shallower for phyto-oestrogen consumers. A previous study had already shown that the ability of the selective oestrogen receptor modulator (SERM) tamoxifen to affect SWAP sensitivities as a function of its duration of use appears to be strongly eccentricity-dependent, with reductions of SWAP sensitivity becoming much more evident at the periphery of the visual field than towards the centre (Eisner et al. 2004a). The present study, which is based on all these considerations, provides a necessary initial step for evaluating the hypothesis that the SWAP hill of vision is shallower for women who consume phyto-oestrogen-rich foods than for women who do not consume these foods.

The present study undertakes this initial step by first classifying women according to whether or not they consume soy and/or flax products and then comparing across these two subject groups the change of visual field sensitivity from the centre to the periphery of the visual field. Soy, which provides isoflavones, and flaxseed, which provides lignans, are the two main sources and classes of phyto-oestrogens in the Western diet (Dixon 2004; Thompson et al. 2006). The SWAP visual field data obtained for this noninterventional study are analysed in their own right, and also against the corresponding data from white-on-white visual fields, to provide multiple means for testing the central hypothesis that the SWAP hill of vision is characteristically shallower for women who consume phyto-oestrogen-rich foods than for women who do not.

Methods

Subjects

Subjects for this study met the same eligibility criteria as did the subjects for an earlier visual field study (Eisner et al. 2006b) that used a four-factor multivariate linear regression model (three visual function factors plus a pupil size factor) to account for SWAP – W/W differences in the periphery of the visual field for healthy women. In fact, the subjects for the present study included all 26 subjects for that previous study plus additional subjects recruited later. Subjects were healthy amenorrhoeic (peri- or postmenopausal) women not using any hormonally acting medications. Because amenorrhoea was denoted by the absence of menses for six consecutive months, it is possible that every subject was postmenopausal, as the 12-month menses-free criterion usually employed for defining menopause is applied retroactively to denote the start of the postmenopausal stage (Harlow et al. 2007).

All subjects passed a stringent set of criteria for excellent ocular health, which included 20/20 visual acuity or better in the test eye and no worse than 20/25 in the other eye. No subject had diabetes or high myopia, and every subject had normal appearing retinas and optic nerve heads, and normal intraocular pressures. All subjects passed a screening test for normal colour vision, as assessed for each eye separately using a D-15 test administered under standard illuminant C, which is the light provided by Macbeth Easel Lamp illumination (no longer manufactured). These and additional eligibility criteria have been detailed previously [e.g. (Eisner et al. 2006b)]. Subjects were volunteers who served as control subjects for several studies concerning effects of breast cancer medications on the eye (Eisner et al. 2006a, 2007, 2008, 2009) and vision (Eisner & Incognito 2006; Eisner & Toomey 2008), but whose data were also analysed in their own right (Eisner et al. 2006b; Eisner & Toomey 2008). None of the subjects for any studies was paid, as many women are highly motivated to contribute to breast cancer research and we wished to eliminate any monetary motivation. Most subjects responded to recruitment ads specifying the requirement of 'normal reading vision (corrective lenses OK)'. Advertisements were placed on electronic sites or in locations where breast cancer survivors specifically, or women in

general, receive health information or health care. Advertisements were also placed in the local newspaper and on the Oregon Health & Science University (OHSU) website for study opportunities. Some subjects were referred by subjects tested previously. All subjects gave written informed consent prior to enrolling in the study and after explanation of the nature and possible consequences of the study. This study was approved by the OHSU Institutional Review Board, and it followed the guidelines of the Helsinki Declaration.

A total of 48 eligible amenorrhoeic subjects were tested, ranging in age from 48 to 69 years. The mean age was 58.1 years (SD = 5.2). The lower and upper inclusive age limits for all subjects had been set beforehand at 40 and 69 years. Menopause below 40 years is atypical (Weinstein et al. 2003), and because visual acuity often starts declining at about 70 years (Haegerstrom-Portnoy et al. 1999), older subjects meeting the 20/20 visual acuity criterion would not necessarily be representative for their age.

Procedures

Choice of test eye

For each subject, one eye was used for all visual field testing. This eye was chosen according to the following three-step procedure, applied in order as necessary: (1) the eye with the better best-corrected acuity; (2) the eye with the lesser degree of spherical equivalent refractive error; and (3) subject preference.

Visual field testing and routine data analysis

All visual field testing was conducted using a single Humphrey Field Analyzer II model 750i instrument (Carl Zeiss Meditec, Dublin, CA, USA) that is serviced yearly and has always met specifications for correct performance. For each subject, two visual field tests were administered, each using a 24-2 test pattern. A white-on-white visual field test was administered first, using a Swedish Interactive Threshold Algorithm (SITA Standard). Full Threshold SWAP fields were administered second, after subjects had rested for about 5 min and then adapted to the yellow background for 3 min. All visual function testing was conducted using conventional procedures [e.g. with optical correction, with size III spots (0.43° diameter) for white-on-white fields and size V spots (1.72° diameter) for SWAP and with stimulus durations always being 200 ms].

We recorded both the raw and age-referenced sensitivity data for each of the two types of visual fields, as provided by the STATPAC© interpretation package running on the Humphrey Field Analyzer. For each testing locus in the visual field, the 'total deviation' is defined as the sensitivity difference from an average age-referenced norm for that type of visual field. The total deviation values are based on proprietary normative population data obtained by the manufacturer and used within STATPAC©. In essence, a total deviation value of zero for a subject of a given age corresponds to a sensitivity equal to the manufacturer's interpolated healthy population mean for that age; positive values correspond to age-referenced sensitivities above that mean and negative values correspond to age-referenced sensitivities below that mean. These norms are not gender-specific, and they presumably did not take hormone use or hormonal status into account. We also refer in this paper to the 'pattern standard deviation' (PSD), which is a measure routinely provided by the STATPAC© package for summarizing the degree to which the visual field contains local or regional departures from age-referenced norms. Large PSD values typically signify that the visual field is either abnormal or unreliable.

For analysis purposes, we subdivided each visual field into four rings, defined on the basis of each ring's distance from fixation (i.e. from the centre of the visual field). Ring 1 consisted of the four visual field loci with x and y co-ordinates at 3° (distance from fixation = 4.2°); ring 2 consisted of the twelve loci with co-ordinates at 9° and 3°, or at 9° and 9° (distance from fixation = 9.5° or 13.8°); ring 3 consisted of the twelve loci with co-ordinates at 15° and 3°, or at 15° and 9° (distance from fixation = 15.3° or 17.5°) and ring 4 consisted of the twenty loci with co-ordinates either at 15° and 15°, at 21° and 3°, or at 21° and 9° (distance from fixation = 21.2°, 21.2°, or 22.8°). The positions in the visual field that corresponded to the blind spot and to its mirror image across the vertical meridian were omitted from the calculations, as were the two most peripheral testing loci, each at about 27° eccentricity in the nasal visual field. For discussion purposes, the outermost ring is considered to represent the periphery of the 24-2 visual field. This subdivision is identical to one we used previously (Eisner et al. 2006b).

We also subdivided the visual field into four quadrants (superior nasal, superior temporal, inferior nasal and inferior temporal) and four hemifields (superior, inferior, nasal and temporal). The same set of data points was used for assigning data to quadrants and hemifields as was used for assigning data to rings.

For each subdivision (e.g. for Rings 1 and 4, which are featured for this paper), the data were averaged across all the testing loci in that subdivision. Thus, the average total deviations for each subject were derived from 4, 12, 12 and 20 data points for Rings 1, 2, 3 and 4, respectively. The quadrant and hemifield data were derived from 12 and 24 data points, respectively.

Dietary information

Each subject was asked, 'On average, how many servings of soy or flax products do you eat or drink per day?' This information was requested in the course of administering a personal-data questionnaire that included medical history information (Eisner et al. 2008). Twenty-four women (the soy/flax consumers) responded to the question with a nonzero value and 24 women (the soy/flax nonconsumers) responded with a value of zero. This 50% split did not reflect any previously determined expectation or criterion. The mean age of the soy/flax consumers was 57.1 years (SD = 5.5), and the mean age of the soy/flax nonconsumers was 59.0 years (SD = 4.9).

Statistical analyses

The analyses focus on the main aim of the study, expressed in the final paragraph of the Introduction. Thus, the analyses are constructed to provide a robust prospective assessment of the hypothesis that soy/flax consumers have characteristically shallower SWAP hills of vision than do

nonconsumers. This single hypothesis was assessed in multiple ways (e.g. by comparing SWAP total deviations, by comparing raw (i.e. non-age-referenced) SWAP sensitivities and also by comparing SWAP – W/W total deviation differences) to control for a variety of potential artifacts. Because a single hypothesis was tested with the requirement that all assessments be significant, no adjustments have been made for the use of multiple tests of statistical significance.

All p-values reported in this paper are based on two-sided tests, and statistical significance is set at $p = 0.05$. Most tests involved the use of parametric statistics, such as *t*-tests, which were conducted using separate rather than pooled variances for between-group comparisons. For one analysis, a 2×2 table was assessed for significance using a Fisher exact test. The parametric analyses included the use of between-group, one-way, repeated-measures analyses of variance (ANOVAS), with the scores for the four different rings regarded as the repeated measures, and with a significant interaction (between-group and ring) interpreted as reflecting a differential effect of subject group on the slope of the hill of vision.

Results

The results that follow are based on the data of the 44 subjects with normal white-on-white PSDs (mean = 1.58 dB, SD = 0.34 dB, maximum = 2.26 dB). The white-on-white PSDs of the four excluded subjects all were 3.26 dB or greater, indicating that these subjects' visual field data were either abnormal or unreliable. The SWAP PSDs of the 44 subjects were unexceptional (mean = 2.93 dB, SD = 0.71 dB, maximum = 4.86 dB) and were higher than the corresponding white-on-white PSDs, as expected. Among these 44 subjects, there were 24 soy/flax consumers [mean age = 57.1 years (SD = 5.5)] and 20 soy/flax nonconsumers [mean age = 58.9 years (SD = 4.6)]. The 1.8-year age difference was not significant ($p = 0.27$, unpaired *t*-test). Finding all four subjects with high white-on-white PSDs to be nonconsumers was not statistically significant ($p = 0.11$, Fisher exact test).

Relations between SWAP and diet: differences between soy/flax consumers and nonconsumers

For the remaining 44 subjects, we found that the slopes of the SWAP hill of vision were characteristically shallower for women who reported consuming soy and/or flax products than for women who reported not consuming these products Furthermore, the effects were small or absent for white-on-white visual fields, and it appeared that the shallowness of the SWAP hill of vision reflected increases of SWAP sensitivity in the periphery rather than decreases in the centre. The data on which these statements are based are presented in the remainder of this subsection.

Because in our previous study (Eisner et al. 2006b), we sought to model SWAP – W/W differences in the periphery of the visual field, the 'eccentricity factor' (i.e. the factor expressly capturing the rate of sensitivity reduction with increasing eccentricity) was necessarily defined using visual field data from closer-in eccentricities, where the effects of eccentricity are quite incomplete. However, for the present study, it is appropriate to emphasize the more complete effects of eccentricity that span the visual field from its centre (Ring 1) to its periphery (Ring 4). Most of the analyses that follow are based on age-referenced sensitivities, that is on the 'total deviations', that are used routinely for clinical assessment of visual field data.

The reduction in average total deviation from the centre (Ring 1) to the periphery (Ring 4) of the SWAP visual field is graphed versus age in Fig. 1 for all 44 subjects, with soy/-flax consumers (filled symbols) distinguished from soy/flax nonconsumers (unfilled symbols). Overall, the reduction with eccentricity was significantly less for the soy/flax consumers than for the nonconsumers ($p = 0.018$). Furthermore, this between-group difference appeared to be specific or predominant for SWAP. That is, there was little between-group difference for white-on-white fields (mean reduction = 0.24 dB greater for nonconsumers, $p = 0.41$), and moreover, the SWAP – W/W difference from Ring 1 to Ring 4 differed

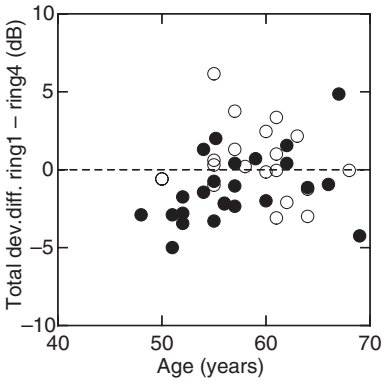

Fig. 1. The reduction of the average total deviation from Ring 1 (mean eccentricity = 4.2° from fixation) to Ring 4 (mean eccentricity = 21.9° from fixation) for Short-Wavelength Automated Perimetry (SWAP) visual fields plotted versus age for each of the 44 subjects. Filled symbols represent soy/flax consumers; unfilled symbols represent soy/-flax nonconsumers. Horizontal dashed line at 0 dB represents the general population normative mean, which is incorporated into the definition of the total deviation (see Methods). Similarly, negative values on the ordinate signify that the reduction of SWAP sensitivity from Ring 1 to Ring 4 was less than the normative age-referenced mean.

significantly between-groups ($p = 0.032$). The difference of raw SWAP sensitivities (i.e. prior to age-referencing) from Ring 1 to Ring 4 yielded significant results ($p = 0.012$) similar to those based on the total deviations. By requiring that all three sets of comparisons be statistically significant, it is possible to control for any artifacts due to differences in the normative databases used for the different visual fields.

An alternative approach for evaluating differential effects of subject group on the slope of the hill of vision is to take all eccentricities into account, which may be performed using a repeated-measures ANOVA as described in the last sentence of the Methods. The results of this ANOVA reaffirm the results derived from comparisons of Rings 1 and 4 only. That is, the interaction term (see Methods) was significant ($p = 0.020$) for the ANOVA conducted using only the SWAP total deviations. Moreover, the corresponding interaction terms for the ANOVAS using either the SWAP – W/W total deviation differences ($p = 0.035$) or the raw SWAP scores themselves ($p = 0.010$) were significant also. In summary, the primary

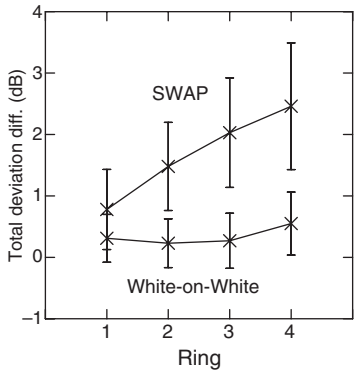

Fig. 2. The mean between-group differences (soy/flax consumers – soy/flax nonconsumers) for the average total deviations for each of the four rings, for Short-Wavelength Automated Perimetry (SWAP) and white-on-white fields separately. The mean eccentricities of Rings 1–4 were 4.2°, 10.9°, 16.8°, and 21.9°, respectively. Error bars are calculated as the square root of the sum of the squares of each group's standard error of the mean for that Ring and that type of visual field. The increase of the values from Ring 1 to Ring 4 for SWAP means that the difference between soy/flax consumers and nonconsumers became progressively greater as retinal eccentricity increased, with the soy/flax consumers being more sensitive than the nonconsumers after age-referencing.

null hypothesis of this study is rejected for all candidate analyses, and it is safe to conclude that overall the soy/flax consumers tended to have shallower SWAP hills of vision than did the nonconsumers.

The mean between-group differences for all 44 subjects are shown graphically as a function of eccentricity (i.e. for each of the four Rings) in Fig. 2 for the SWAP and W/W total deviations separately. These between-group differences can be seen to vary more with eccentricity for SWAP visual fields than for white-on-white visual fields. This differential was greatest for Ring 4, where the SWAP total deviation averaged 2.46 dB greater for the soy/flax consumers than for the nonconsumers ($p = 0.022$). Any between-group differences for white-on-white fields were quite small, with the largest such difference being 0.55 dB at Ring 4. These data are presented numerically in Table 1, along with the corresponding SWAP – W/W difference data.

Additional observations

The importance of retinal locus did not appear to extend to divisions of the visual field other than those defined by eccentricity. In particular, no large or even nominally significant between-group differences were observed to exist as a function either of retinal hemifield or retinal quadrant. For example, the nasal – temporal SWAP total deviation difference was about 0 dB for each group; it was 0.15 dB for the soy/flax consumers and −0.13 dB for the soy/flax nonconsumers. The magnitude of the superior – inferior SWAP total deviation difference was more pronounced (0.74 dB for the soy/flax consumers versus 0.00 dB for the soy/flax nonconsumers) but even this larger magnitude difference did not approach significance. Moreover, the between-group effect shrunk from 0.74 to 0.35 dB when the SWAP – W/W difference was considered.

Although none of the between-group differences for white-on-white visual fields approached significance for any of the rings, the small (0.55 dB) between-group difference observed for Ring 4 might not have been because of chance. The PSD for white-on-white fields was less for soy/flax consumers than for nonconsumers (mean PSD = 1.46 dB versus 1.72 dB, $p = 0.012$), and furthermore, the reduction of the average total deviation difference from Ring 1 to Ring 4 for white-on-white fields correlated significantly with the PSD for white-on-white fields ($r = 0.54$, $p < 0.001$). The corresponding analyses for SWAP fields were likewise significant. Bear in mind that the four subjects with high outlying white-on-white PSDs have been excluded from these analyses.

All the results described thus far are based on assignment of subjects into one or the other of two groups: soy/flax consumers and soy/flax nonconsumers. We also examined the data for ostensible dose-dependent relations, that is for relations involving the reported number of daily soy and/or flax servings, but no relations were discerned. This could be because the majority (54%) of soy/flax consumers reported averaging one serving per day. In addition, phyto-oestrogens may be obtained in minor amounts from a variety of food sources (Thompson et al. 2006), with bioactive levels differing between individuals depending on the presence of certain gut bacteria (Atkinson et al. 2005; Lampe et al. 2006).

Table 1. Total deviation differences between consumers and nonconsumers.

	N	Ring 1	Ring 2	Ring 3	Ring 4
SWAP	44	0.77 ± 0.66	1.49 ± 0.72	2.03 ± 0.89	2.46 ± 1.03
White-on-white (W/W)	44	0.31 ± 0.38	0.24 ± 0.40	0.27 ± 0.45	0.55 ± 0.51
SWAP – W/W	44	0.46 ± 0.60	1.25 ± 0.61	1.76 ± 0.75	1.91 ± 0.83

SWAP, Short-Wavelength Automated Perimetry.
The average total deviation data for the 24 soy/flax consumers minus the average total deviation data for the 20 soy/flax nonconsumers for each of the four Rings: Ring 1 (mean eccentricity = 4.2° from fixation), Ring 2 (mean eccentricity = 10.9° from fixation), Ring 3 (mean eccentricity = 16.8° from fixation), and Ring 4 (mean eccentricity = 21.9° from fixation) for SWAP visual fields. Line 1 is for SWAP, line 2 is for white-on-white (W/W) visual fields, and line 3 is for the corresponding SWAP – W/W differences. Error terms for SWAP and W/W fields alone are calculated as the square root of the sum of the squares of each group's standard error of the mean for that Ring and that type of visual field. Error terms for the SWAP – W/W difference are calculated in the corresponding way after first calculating the SWAP – W/W difference data for individuals.

Discussion

The study described in this paper aimed to provide a necessary first step for addressing the hypothesis that the SWAP visual fields of postmenopausal women who consume phyto-oestrogen-rich foods differ characteristically from the SWAP visual fields of women not consuming these foods. The results – that the slopes of the SWAP hill of vision were shallower for women who reported consuming soy and/or flax products than for women who reported not consuming these products – supported this idea, and in doing so, they provide reason for

conducting further observational studies in which fuller dietary and medical history information is obtained and for which the levels of various specific isoflavones and lignans (Dixon 2004) are measured (Lampe 2003) and compared with indices of SWS-cone-mediated response. Such studies still would not suffice to prove that dietary factors caused visual response to change, but depending on the outcome of such studies, they could provide the justification for subsequent dietary interventional studies that would suffice to establish causality. At the same time, effects of medications designed to alter oestrogen levels should be evaluated in controlled studies wherein women are tested while using their medication and while not.

New clinical applications for SWAP

Our study is not the first to suggest an application for SWAP outside its original intended purpose as a glaucoma test. In particular, SWAP deficits have been shown to correlate with reductions of retinal capillary density at the centre of the macula caused by diabetes (Remky et al. 2000; Bengtsson et al. 2005), and there is evidence that SWAP may provide a means for assessing visual dysfunction arising from other circulatory disturbances, such as those that cause migraine (McKendrick et al. 2002) or that may accompany macular degeneration (Remky et al. 2005). In addition, the present study is one in a line of studies, cited in the Introduction, suggesting that hormonal change can affect either SWAP or SWS-cone-mediated response more generally. In this regard, we call the reader's attention to the growing use of aromatase inhibitors (AIs), a relatively new class of medications that virtually abolish oestrogen synthesis in people without ovarian function (Geisler & Lonning 2005; Santen et al. 2009). Aromatase inhibitors are becoming the adjuvant endocrine therapy of choice for postmenopausal women with early-stage-hormone-receptor-positive breast cancer (Lonning 2007), so given the demographics of breast cancer (Feuer et al. 1993; Chu et al. 2001), AI usage is becoming very common.

Sources of variability for SWAP

A major aim of the present study was to test the premise that some of the sources of between-subject and within-subject variability in SWAP are more systematic than previously recognized. The results supported this premise in that the answer to a simple prospective dietary question was shown to relate characteristically to the degree by which SWAP sensitivities change with eccentricity. The lack of a corresponding dietary association for more conventional white-on-white visual field sensitivities could mean that the underlying effect is specific for SWS-cone-mediated response. However, it is also possible that similar effects exist for non-SWS-cone visual pathways but were not observed because the stimulus parameters used for white-on-white visual field testing are not well suited for this purpose; the stimulus durations may be too long or the stimulus sizes too small, for instance. Alternatively, it is possible for a substantial sensitivity change occurring within one visual pathway to have been masked by intrusion from a different visual pathway, because any of several visual mechanisms with similar sensitivities is capable of detecting the stimuli used for white-on-white visual fields (Harwerth et al. 1993).

Some of the causes of SWAP variability have long been appreciated [e.g. concerning lens density (Sample et al. 1994)] or have been predicted and documented more recently [e.g. concerning visual adaptation (Eisner et al. 2006b; Felius & Swanson 2003)]. Lens density, however, would have little effect on the rate at which SWAP sensitivity changed with eccentricity. The degree of desensitization induced by the yellow SWAP adapting background is expected to vary at least somewhat with eccentricity (Pearson & Swanson 2000), although how such variation would be related to any of the nonvision factors underlying the results of the present study is unknown. Additional factors that are likely to impact the rate at which SWS-cone-mediated sensitivity changes with eccentricity include eccentricity-dependent increases in spatial summation and response convergence (Pearson et al. 2006; Beirne et al. 2008), eccentricity-dependent changes in the strengths of on-signalling versus off-signalling pathways (Vassilev et al. 2003) and attentional variables. The spatial integration properties of SWS-cone-mediated on- and off-responses have been shown to differ more in the periphery of the visual field than in the centre (Vassilev et al. 2003) in such a way that makes it possible for SWAP stimuli in the periphery of the visual field to be sometimes detected more via their offset than via their onset.

There is at least one additional factor that is known to affect the rate at which some measures of SWS-cone-mediated sensitivity change with eccentricity (Swanson et al. 2008) and is likely to impact the rate at which SWAP sensitivity changes with eccentricity. This factor concerns temporal response, particularly as it affects temporal integration.

The visual field testing device used for this study (a Humphrey Field Analyzer) employs 200-ms duration stimuli that were chosen originally for SWAP on the basis of several considerations. First, because the saccadic latency is greater than about 200 ms (Fendrich et al. 1999), the choice of 200 ms as the stimulus duration facilitates proper fixation and reduces the impact of poor fixation should it occur. Second, because 200 ms greatly exceeds the temporal integration periods for detection of achromatic incremental stimuli (King-Smith & Carden 1976; Smith et al. 1984), it would tend not to interact with individual differences in those integration periods. The original choice of 200 ms as the stimulus duration for white-on-white automated perimetry took both of these considerations into account. For SWAP, however, 200 ms is closer to the normal integration period, and in fact, data obtained for a six-subject study (Sample et al. 1996) revealed that some temporal integration occurs beyond 200 ms. Thus, the choice of 200 ms as the SWAP stimulus duration involved a compromise among competing practical and theoretical considerations. A more recent two-subject study (Swanson et al. 2008) showed that temporal integration periods for SWS-cone-mediated vision can appreciably exceed 200 ms, and furthermore, depend substantially on

retinal eccentricity, being much longer nearer the fovea than at 21° eccentricity. This dependence would be expected to cause between-subject differences or within-subject changes in temporal integration periods to affect SWAP sensitivities differentially in the periphery versus the centre of the visual field. The effects would often be greater in the periphery, where changes in temporal integration periods would be proportionally larger relative to 200 ms.

Effects of oestrogen on the CNS: a new perspective

Although temporal response is but one of several salient factors that could be affected by or be associated with soy/flax consumption, there are two additional reasons for singling out this particular factor. First, any lifestyle factors or agents that affect visual temporal response properties may be expected to affect the temporal response properties of at least some other neural systems also. This generality contrasts with effects on visual response properties that pertain exclusively or inherently to retinal eccentricity. Second, we have provided evidence, based mostly on foveal data, that reduced oestrogen activity can lead to reductions in response gain and/or temporal response speed (Eisner & Toomey 2008). If oestrogen-dependent alterations exist in the temporal response properties of one or more visual pathways, it would be remarkable if such alterations did not occur at any other sites or networks in the CNS, which is replete with oestrogen receptors even outside the reproductive axis (Simpson 2003; Garcia-Segura 2008; Morissette et al. 2008). Alpha and beta oestrogen receptors each are present in the retina (Munaut et al. 2001).

Because the visual system is a uniquely accessible part of the CNS that responds in highly quantifiable ways to stimuli that can be precisely controlled, appropriately chosen measures of visual response have promise for providing a practical means for evaluating effects of oestrogen loss or of oestrogen surrogates on neural function. This promise should be considered in the context of a prominent new concept in the women's health literature, known as the 'timing hypothesis' (Manson & Bassuk 2007) or the 'critical period hypothesis' (Sherwin & Henry 2008), which postulates that the positive effects of supplemental oestrogen are strongly age-related, with the benefits occurring only for women using such supplementation before too long a period of time has elapsed since menopause. In this regard, a re-examination of Fig. 1 suggests that an age effect may have existed for this study, as the reduction in the average total deviation from Ring 1 to Ring 4 for SWAP was observed to increase with age for the 24 soy/flax consumers (Spearman $r = 0.46$), but not for the 20 soy/flax nonconsumers (Spearman $r = -0.23$). The corresponding results for the SWAP – W/W difference were similar, and there was no evidence for a corresponding effect for white-on-white fields. These observations need to be re-examined in a prospective, adequately powered, study that also records subjects' dates and types of menopause.

SWAP norms and nonpathologic change

In addition to their potential biological importance, the effects reported in this paper are important operationally because they indicate that the norms supplied by the manufacturer and used to assist with interpreting SWAP test results may be too broadly applied. Nevertheless, if the regional SWAP visual field differences observed between groups of women for this study occurred over a relatively short period of time for an individual, identifying a potential nonophthalmologic cause or factor (e.g. because of a change in diet or hormonal exposure) could help alleviate clinical suspicion. This would be beneficial for any SWAP application.

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