

Luis Teixeira, M.D.

Hôpital Saint-Louis
75010 Paris, France
luis.teixeira@inserm.fr

Cedric Julien, Ph.D.

INSERM Unité 567
75014 Paris, France

Fabien Guimiot, Ph.D.

Hôpital Robert Debré
75019 Paris, France

1. Estivill X, Armengol L. Copy number variants and common disorders: filling the gaps and exploring complexity in genome-wide association studies. *PLoS Genet* 2007;3:1787-99.
2. Stranger BE, Forrest MS, Dunning M, et al. Relative impact of nucleotide and copy number variation on gene expression phenotypes. *Science* 2007;315:848-53.

TO THE EDITOR: Pharoah et al. report on seven polymorphic markers for breast-cancer risk replicated in genomewide-association studies. Although it is well known that cases of premenopausal and postmenopausal breast cancer have different risk factors, these cases were analyzed as one group. Polymorphisms may alter gene expression, but expression is also regulated by environmental factors, which may lead to epigenetic changes.¹ The magnitude of risk modification may be miscalculated when premenopausal and postmenopausal patients are combined and no questionnaire data on relevant environmental risk factors are considered. For example, the protective effect of caf-

feinated coffee on hereditary and sporadic breast cancer appears to be substantial but limited to women with the CYP1A2*1F C allele.^{2,3} CYP1A2 is a key enzyme in caffeine and estrogen metabolism.⁴ It is biologically plausible that various combinations of genetic and nongenetic factors (e.g., coffee) that regulate CYP1A2 expression⁵ affect risk differently. Combining data from questionnaires and genomewide-association studies in which premenopausal and postmenopausal patients are stratified may yield better risk estimates for the selection of women for screening.

Helena Jernström, Ph.D.

Lund University
SE-221 85 Lund, Sweden
helena.jernstrom@med.lu.se

1. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 2007;27:363-88.
2. Kotsopoulos J, Ghadirian P, El-Sohehy A, et al. The CYP1A2 genotype modifies the association between coffee consumption and breast cancer risk among BRCA1 mutation carriers. *Cancer Epidemiol Biomarkers Prev* 2007;16:912-6.
3. Bågeman E, Ingvar C, Rose C, Jernström H. Coffee consumption and CYP1A2*1F genotype modify age at breast cancer diagnosis and estrogen receptor status. *Cancer Epidemiol Biomarkers Prev* 2008;17:895-901.
4. Lee AJ, Cai MX, Thomas PE, Conney AH, Zhu BT. Characterization of the oxidative metabolites of 17beta-estradiol and estrone formed by 15 selectively expressed human cytochrome p450 isoforms. *Endocrinology* 2003;144:3382-98.
5. Djordjevic N, Ghotbi R, Bertilsson L, Jankovic S, Aklillu E. Induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes. *Eur J Clin Pharmacol* 2007;64:381-5.

Graves' Disease

TO THE EDITOR: In his Clinical Practice article on Graves' disease, Brent (June 12 issue)¹ comments on the combined use of antithyroid drugs and radioiodine and refers to the results of our trial,² showing no effects of antithyroid drugs on radioiodine therapy after a 3-day-withdrawal. However, in a subsequent meta-analysis,³ we found that antithyroid drugs significantly reduced the success of radioiodine therapy, even when the drugs were discontinued for a week. This conclusion contradicted those of most of the included trials (including our own), which were most likely underpowered to detect significant differences. We now discontinue antithyroid drugs for more than a week before radioiodine therapy, if clinically feasible. Adequately powered trials are needed to better inform this issue.

Martin A. Walter, M.D.

Mirjam Christ-Crain, M.D.

Beat Muller, M.D.

University Hospital
CH-4031 Basel, Switzerland
m.a.walter@gmx.net

1. Brent GA. Graves' disease. *N Engl J Med* 2008;358:2594-605.
2. Walter MA, Christ-Crain M, Schindler C, Müller-Brand J, Müller B. Outcome of radioiodine therapy without, on or 3 days off carbimazole: a prospective interventional three-group comparison. *Eur J Nucl Med Mol Imaging* 2006;33:730-7.
3. Walter MA, Briel M, Christ-Crain M, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007;334:514.

TO THE EDITOR: As noted by Brent and others,¹ thyroid volume, circulating titers of thyrotropin-receptor antibodies, sex, and age are predictors

of remission in Graves' disease and are commonly used as indicators for choosing the best therapeutic option. However, several studies²⁻⁴ have shown that an older age at presentation and not the contrary, as stated by Brent, characterizes patients with Graves' disease who are most likely to undergo a prolonged remission after treatment with antithyroid drugs. Thus, especially in patients with Graves' disease who are older than 40 years, a full course of antithyroid drugs is a reasonable therapeutic option, which could avoid unnecessary thyroid surgery, radioiodine ablation, or both, with the subsequent need for lifelong levothyroxine treatment.

Mario Rotondi, M.D., Ph.D.

Rodolfo Fonte, M.D.

Luca Chiovato, M.D., Ph.D.

Fondazione S. Maugeri IRCCS
27100 Pavia, Italy

1. Cooper DS. Antithyroid drugs. *N Engl J Med* 2005;352:905-17.
2. Yamada T, Aizawa T, Koizumi Y, Komiya I, Ichikawa K, Hashizume K. Age-related therapeutic response to antithyroid drug in patients with hyperthyroid Graves' disease. *J Am Geriatr Soc* 1994;42:513-6.
3. Vitti P, Rago T, Chiovato L, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid* 1997;7:369-75.
4. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab* 2000;85:1038-42.

TO THE EDITOR: Brent does not discuss the adverse effects of cigarette smoking in patients with Graves' disease. Research findings support associations between cigarette smoking and both Graves' disease and Graves' ophthalmopathy. For example, a meta-analysis showed an odds ratio for Graves' disease of 3.30 (95% confidence interval [CI], 2.09 to 5.22, based on data from eight studies) among current smokers as compared with persons who had never smoked.¹ The meta-analysis also showed that the odds ratio for Graves' ophthalmopathy among persons who had ever smoked was 4.40 (95% CI, 2.88 to 6.73, based on data from six studies). Among current smokers, the hazard ratio for Graves' disease increases with the intensity of smoking.²

Cigarette smoking is also associated with a higher degree of severity in Graves' ophthalmopathy and a lower effectiveness of medical treatment.³ Cigarette smoking increases the risk of

progression of ophthalmopathy after radioiodine therapy and decreases the efficacy of orbital radiation therapy and glucocorticoid therapy.⁴

Therefore, clinicians treating patients with Graves' disease, including those with Graves' ophthalmopathy, should strongly advise these patients not to smoke cigarettes and, wherever possible, to avoid exposure to environmental tobacco smoke.

Barry S. Levy, M.D., M.P.H.

Tufts University School of Medicine
Boston, MA 02111
blevy@igc.org

1. Vestergaard P. Smoking and thyroid disorders — a meta-analysis. *Eur J Endocrinol* 2002;146:153-61.
2. Holm IA, Manson JE, Michels KB, Alexander EK, Willett WC, Utiger RD. Smoking and other lifestyle factors and the risk of Graves' hyperthyroidism. *Arch Intern Med* 2005;165:1606-11.
3. Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid* 2002;11:855-60.
4. Bartalena L, Marcocci C, Tanda ML, et al. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. *Ann Intern Med* 1998;129:632-5.

TO THE EDITOR: Brent refers to a study we performed to support the claim that no increased risk of cancer has been reported after treatment with radioactive iodine in patients with Graves' disease. On the contrary, we have reported an increased risk of cancer both among patients with Graves' disease and among those with toxic multinodular goiter.¹ The incidence of cancers of the stomach, kidney, and breast was increased. However, the increase in overall and cancer-related mortality was seen only among the patients with toxic multinodular goiter, who were older than the patients with Graves' disease.² We recommend that the small but significant risk of cancer should be considered in planning the treatment for hyperthyroidism, at least in children and young adults.

Saara Metso, M.D.

Tampere University Hospital
33520 Tampere, Finland
saara.metso@uta.fi

Pia Jaatinen, M.D., Ph.D.

University of Tampere
33014 Tampere, Finland

Jorma Salmi, M.D., Ph.D.

Tampere University Hospital
33520 Tampere, Finland

1. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P.

Increased cancer incidence after radioiodine treatment for hyperthyroidism. *Cancer* 2007;109:1972-9. [Erratum, *Cancer* 2007;110:1875.]

2. Metso S, Jaatinen P, Huhtala H, Auvinen A, Oksala H, Salmi J. Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. *J Clin Endocrinol Metab* 2007;92:2190-6. [Erratum, *J Endocrinol Metab* 2007;92:4008.]

THE AUTHOR REPLIES: Walter and colleagues detected an influence of antithyroid-drug treatment on the effectiveness of radioiodine therapy in their meta-analysis,¹ although half the studies included did not discontinue the antithyroid drug before radioiodine therapy; the effectiveness of radioiodine therapy was also improved with higher doses of radioiodine.¹ Their practice of discontinuing antithyroid drugs for more than 1 week before administering radioiodine is at the limit of the range of 3 to 7 days recommended in the review and by most clinical guidelines. The risk of a prolonged interval of antithyroid-drug cessation is worsening hyperthyroidism, which is clinically relevant primarily for patients with more severe hyperthyroidism or increased susceptibility, such as those with active cardiac disease. I concur with the recommendation for an adequately powered trial.

Rotondi and colleagues correctly state that younger patients with Graves' disease are less likely to have a remission with antithyroid-drug therapy; I regret the error. The study cited in the review² showed that patients with Graves' disease who were less than 40 years old had a lower remission rate after long-term antithyroid-drug treatment (32.6%) than patients who were 40 years or older (47.8%). Younger patients, as compared with older patients, have higher levels of thyrotropin-receptor antibodies and the associated manifestations of increased thyroid volume and increased thyroid hormone levels, especially serum triiodothyronine.

Levy emphasizes the important role of cigarette smoking in Graves' disease, especially Graves' ophthalmopathy. Patients should be informed that cigarette smoking is likely to worsen ophthalmopathy and reduce the response to treatment. Most studies have shown a cigarette dose effect, so a reduction in the number of cigarettes

smoked may also be beneficial. Smoking is also associated with a larger goiter at presentation among patients with Graves' disease and a reduced likelihood of remission with antithyroid drugs.³

Metso and colleagues refer to the association of cancer with radioiodine therapy for hyperthyroidism. The references cited in the review from their group and others focused on cancer-related mortality after radioiodine therapy, and this should have been clarified in the discussion. Metso and colleagues report a small but significant dose-related increase in the incidence of stomach, kidney, and breast cancers in long-term follow-up of patients with hyperthyroidism who received treatment with radioiodine.⁴ A larger series⁵ showed an overall reduction in the incidence of cancer among patients treated with radioiodine for hyperthyroidism but an increase in the incidence of a few cancers. The finding, from several long-term studies, of no increase in cancer-related mortality after radioiodine treatment for Graves' disease is reassuring. The small increase in the incidence of some cancers, including several potentially linked to direct exposure to or uptake of iodine, may be relevant for treatment decisions.

Gregory A. Brent, M.D.

Veterans Affairs Greater Los Angeles Healthcare System
Los Angeles, CA 90073
gbrent@ucla.edu

1. Walter MA, Briel M, Christ-Crain M, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007;334:514.
2. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab* 2000;85:1038-42.
3. Glinoe D, de Nayer P, Bex M. Effects of L-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study. *Eur J Endocrinol* 2001;144:475-83.
4. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. *Cancer* 2007;109:1972-9. [Erratum, *Cancer* 2007;110:1875.]
5. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 1999;353:2111-5.