**Table 1.** ***RRM1*** **Coding-Region Variations in Non–Small-Cell Lung Cancers.**

| Patient No. | 249 G→A Arg/Gln | 568 C→T His/His | 733 A→C Pro/Pro | 768 A→C His/Pro | 821 T→G Trp/Gly | 871 A→G Pro/Pro | 1082 A→C Arg/Arg | 2455 A→G Thr/Thr | 2464 A→G Ala/Ala | 2565 T→C Val/Ala |
|---|---|---|---|---|---|---|---|---|---|---|
| D234 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D236 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D245 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D247 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D314 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D352 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D356 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D358 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D366 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D372 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D374 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D376 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |
| D378 | cGa | caC | ccA | cAc | Tgg | ccA | Aga | acG | gcA | gTg |

tion; however, we were unable to show their effect on in vivo gene expression.[2]

We sequenced the coding region of *RRM1* in fresh-frozen specimens from 13 white men and women with non–small-cell lung cancer; at least 70% of the cells in the specimens were tumor cells. Sequences of good quality were compared with NM_001033 (Table 1) and all patient sequences were identical to one another.

We had previously reported an A at position 2455. In all specimens, G was the only nucleotide found at this position. For all other SNPs, we found only the nucleotide reported in the reference sequence. We have noted that the sequence chromatograms for the regions containing the SNPs frequently display low nucleotide signal values. The automated base assignment is often ambiguous in particular when double cytosines or guanines precede or follow the referenced SNPs. These technical limitations may account for the reported SNPs and call their existence into question. Given these limitations, it is our opinion that investigations of the correlations between reported SNPs and clinical outcomes are premature.

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## Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils

**TO THE EDITOR:** The study by Henley et al. (Feb. 1 issue)[1] raises many questions. Product names were not provided. Did the authors contact manufacturers to report concerns or ask about constituents? The variability, adulteration, and contamination of herbal products have been widely reported,[2,3] as have discrepancies between labels and contents.[4] Plastic containers may contain phthalates, known endocrine disrupters.[5] What was actually in the products cited in this report?

None of the hormonal testing showed abnormal results, except in Patient 2, who had elevated levels of testosterone (not estrogen). There was no report on ultrasound examination or needle

biopsy, nor were subsequent weight changes reported. Might the patients' gynecomastia have reflected another pathophysiological process that resolved spontaneously?

Traditional use and clinical trials have not suggested estrogenic effects of tea tree or lavender oil, though estrogenic effects have been reported for other essential oils and plants. Are occupational exposures to lavender and tea tree associated with estrogenic symptoms? In vitro testing alone is not adequate grounds for indicting traditionally used products and may raise public fear.

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**TO THE EDITOR:** Henley et al. do a commendable job of sleuthing out the likely cause of prepubertal gynecomastia in the young boys exposed to either lavender or tea tree oil. However, given that estrogenic compounds have yet to be detected in either oil, it is important that we carefully interpret these important findings. A growing number of endocrine disrupters in our environment have been shown to accumulate in adipose tissue.[1,2] A number of such industrial by-products have also been implicated in early thelarche.[3] Since these molecules with hormone-modulating activity are fat soluble, topically applied oils may serve as very efficient delivery agents for environmental endocrine disrupters by concentrating them and delivering them into cells. Although Henley et al. attempt to show that these oils have estrogenic activity, the results of their reported assays indicate a very weak effect. It would be bewildering if such relatively low hormonal activity alone could instigate prepubertal gynecomastia.

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**TO THE EDITOR:** The evidence in the three case studies by Henley et al. does not support their conclusion. Only one of three boys (Patient 2) was exposed to any amount of tea tree oil, and that subject was also exposed to lavender oil. Patients 1 and 3 used cosmetic products containing lavender oil alone. There is no rational process that could allow the authors to conclude that tea tree oil caused the gynecomastia in Patients 1 and 3 or separate the effects of lavender oil from those of tea tree oil in Patient 2. Thus, how can one reach the conclusion that tea tree oil has any causative role in the observed gynecomastia?

Moreover, the authors make no attempt to correlate the three case studies and the cell-culture assays scientifically. The estrogenic activity expressed in the cell-culture assays was dose dependent. The response was negative at low levels and became positive at levels that corresponded to 600,000 to 1.4 million times the 1 nM level of the positive control, estradiol. It is beyond reason to conclude that the one boy who used a shampoo and hair gel containing a minimal amount of tea tree oil could have been exposed at this high a dose.

Of equal significance is the fact that the testing conducted in this preliminary study was far from comprehensive. The researchers themselves acknowledge that there were other compounds, including other essential oils, in the personal care products used by the boys that the researchers did not test.

If casual exposure to products containing tea tree oil could indeed induce gynecomastia in oth-

erwise normal young males, this effect would have been manifested long ago in the population, given the number of products on the market containing this ingredient. My employer has sold 123 million bottles of cosmetic and household products containing tea tree oil during the past two decades, and it has never received a report of gynecomastia before this study. Although those who have worked with tea tree oil for many years are convinced it does not cause gynecomastia, we do not want to be blind to that remote possibility. If anyone in the medical community becomes aware of any cases involving tea tree oil and gynecomastia, please contact me.

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Dr. Kurtz is an employee of Melaleuca, a company that manufactures and markets personal-care, pharmaceutical, household, and nutritional products, including many products incorporating tea tree oil. No other potential conflict of interest relevant to this letter was reported.

**TO THE EDITOR:** The study by Henley et al. does not support a causative link between the use of products containing minimal amounts of lavender and tea tree oils and gynecomastia in three boys. The study was uncontrolled, with hundreds of other suspect agents — such as soy, licorice, hops, garbanzo beans, lentils, flaxseed, and sunflower seed — possibly having a role. Henley and colleagues' data suggesting that tea tree oil penetrated skin are misleading. Various studies[1] have shown that only 3 of more than 100 compounds enter the skin from 100% pure tea tree oil. In a wash-off product containing less than 1% tea tree oil, the amount would be almost undetectable.

If the study by Henley et al. shows any estrogenic activity of these oils, it is at a level up to 1 millionth that of estradiol, the positive control. Thus, an average 20-kg child would have had to use approximately 40 bottles of shampoo for each application. The claim of a causative link between the use of tea tree oil products and prepubertal gynecomastia appears to be misleading and unwarranted.

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Mr. Dean founded, worked for, and is currently consulting for TP Health, a company that produces a range of tea tree oil products, and is chair of the Technical and Safety Committee of the Australian Tea Tree Oil Industry Association. No other potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** With regard to the comments of Kemper et al.: we were deliberate in not naming commercial products. We did not contact the manufacturers but, rather, found the listed ingredients on the product labels or in the product information on the manufacturers' Web sites. Since these products are available to consumers and fall under federal regulation, it would be illegal for the manufacturers to list the ingredients inaccurately. We are not aware of any systematic study examining estrogenic symptoms from occupational exposure to lavender or tea tree oil. Our study involved boys, not adults. Furthermore, we are not aware of any randomized, controlled clinical trials examining the estrogenic effects of exposure to lavender or tea tree oil in children. We are open to the idea, however, that there may be other essential oils that could have contributed to the clinical findings in our subjects.

We agree with Kalyan that our findings should be interpreted carefully. Again, we are open to the possibility that the estrogenic effects could be modified by other disrupters and encourage further research in this regard. We would remind readers that we observed an unusual clinical phenomenon in prepubertal boys that resolved on discontinuation of the topically applied products.

Kurtz and Dean question our findings, apparently in an effort to defend their commercial interest — namely, the marketing of tea tree oil. Of course our study was uncontrolled. It is highly unlikely that "hundreds of other suspect agents" might have caused the gynecomastia or that the condition would have developed earlier and would not have resolved by discontinuation of the suspected products. We agree that Patient 2 was exposed to lavender oil as well as to tea tree oil. There may be a valid argument that it was the lavender oil that caused the gynecomastia. However, the tea tree oil had activity similar to that of

lavender oil with respect to in vitro estrogenic and antiandrogenic effects. Thus, one could just as easily make the case that the effects of two essential oils were additive in causing the in vivo gynecomastia. We would argue that the hair gel may not have been simply a "wash-off product," as Dean claims, but may instead have remained on the scalp and palms, resulting in prolonged exposure, particularly if washing was incomplete.

We agree that further scientific studies are necessary to answer the questions that the correspondents have posed. Since exact components of the oils have not been identified, any comparison regarding relevant activity cannot be made. Furthermore, we hope that epidemiologic studies will follow and other potential endocrine disrupters will be sought by direct analysis of the essential oils and over-the-counter commercial products.

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## The Failing Heart

**TO THE EDITOR:** The review article by Neubauer (March 15 issue),[1] which focuses on myocardial energetics, states that the use of fatty acids and glucose is decreased and insulin resistance develops in advanced heart failure. Neubauer also suggests some new drug targets for the treatment of heart failure in the peroxisome proliferator–activated receptor (PPAR) family, including PPAR$\alpha$ and PPAR$\gamma$ coactivator 1. We want to add PPAR$\delta$ to the list. PPAR$\delta$ is another isotype of the PPAR family.[2] Cheng et al.[3] discovered that a heart that is deficient in PPAR$\delta$ has decreased fatty acid oxidation and lipotoxic cardiomyopathy, and Planavila et al.[4] showed that activation of PPAR$\delta$ inhibits hypertrophy in cardiomyocytes. A PPAR$\delta$ agonist may increase the oxidation and use of fatty acids and inhibit the remodeling process leading to hypertrophy, cardiomyopathy, and heart failure.

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**TO THE EDITOR:** The review of the biochemical mechanisms of the failing heart did not mention thiamine deficiency and thiamine supplementation in the management of heart failure. Limited studies in patients with heart failure, especially those receiving high-dose loop-diuretic therapy, which can lead to thiamine wasting, have shown that thiamine deficiency occurs in heart failure. Moreover, small randomized trials have shown a benefit of thiamine supplementation at a dose of 200 mg per day.[1-4] In light of the data already available, it is prudent to provide thiamine supplementation in patients with heart failure, and it is important to conduct further studies of its efficacy and safety.

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