early detection may be associated with less morbidity. The article by Welch and Frankel are unfortunate because they promote backward movement by promoting reactive treatment rather than the proactive prevention strategies that have proven to be so effective in reducing breast cancer mortality. Rather than discounting screening benefits, efforts should be directed at improving the safety and sensitivity of breast screening modalities.

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Screen Detection Has Both Winners and Losers

Dr Welch is a pioneer in presenting the benefits and harms of screening to both clinicians and the public. However, Keen and Keen were the first to devise the method to calculate the life-saving proportion (LSP) of screen-detected breast cancers, using matched 15-year periods. The follow-up analysis promoting screening mammography insight used 10-year periods. The higher percentage of screen-detected cancers (61%-64% vs 50%-56%) in the article by Welch and Frankel makes our estimates higher, while the mixed 20-year/10-year death/diagnosis risk makes our estimates lower.

Our screen-free absolute death risk over 15 years at age 50 years is 8.83 (range, 8.1-9.7) per 1000 women. Combining analyses for a mixed 15-year/10-year scenario gives an LSP of 11% vs Welch and Frankel’s 9%, at a 20% relative risk reduction (RRR). With the assumption of a screening trials—based 15% RRR (range 10%-20%), the LSP is 8% (5%-10%) for patients aged 40 to 49 years. The LSP would also be 8% (5%-11%) for patients aged 50 to 59 years and 8% (5%-10%) for patients aged 60 to 69 years. Clearly, the LSP is age independent and at maximum is 1 woman in 10. Jørgensen et al review the improved treatment and breast cancer awareness since the trials, which support a 10% or lower RRR (9 in 10 women with lethal cancers die despite an invitation to screening). Therefore, radiologists must detect more than 20 cancers to prolong 1 life.

From this perspective, screening mammography is a lottery. Regrettably, there are both winners and losers. Before choosing participation, women should know what proportion of screen-detected cancers represents pseudodisease, which turns healthy women into patients with cancer. When a base case overdiagnosis rate of 30% is used, the fraction of pseudodisease is 41% to 46%, depending on patient age. With the assumption that 90% of ductal carcinoma in situ is screen detected and only half progresses, the fraction of pseudodisease is 16% to 18% and equivalent to a 10% overdiagnosis rate. Realistically, allowing for some invasive cancer overdiagnosis with a 20% rate, pseudodisease represents at least 1 in 3 screen-detected cancers (30%-33%).

The pseudodisease ratio (PDR=pseudodisease/lives prolonged) therefore varies from 5:1 to 6:1 (41/8 to 46/8), at a 15% RRR. Half of women with screen-detected breast cancer starting at age 50 years are either harmed (42%) or helped (8%); the other half receiving an early diagnosis with no effect includes the 20% of women who die of breast cancer. Unfortunately, the overdiagnosis rate is more likely on the order of 52% (PDR from 8.1 to 9.1) and is getting worse with new technology. With the benefit shrinking and the harm growing over time, women deserve informed consent before screening. This is best coordinated by clinicians ordering the mammogram to circumvent the inherent conflict of interest of radiologists and other screening advocates (such as http://www.mammographysaveslives.org).

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Dietary Supplements and Mortality

We thank Mursu and colleagues for a well-needed analysis of supplement use in relation to mortality. The findings deserve some thought. When addressing surprising associations like this, we believe one needs to ask questions such as, What kind of people use dietary supplie-
Dietary Supplements and Altered Mortality: A Conflict of Evolutionary Medicine

The findings of Mursu et al\textsuperscript{1} are welcome and support what many nutritional scientists believe, that too little or excess micronutrient intake is detrimental to health. Nutritional wisdom is contemporaneous. During the first half of the 20th century we were concerned with undernutrition and defining deficiency syndromes. From the mid-1970s, this focus shifted to overnutrition and chronic degenerative disorders. Today we seem to be facing up to the excesses of recent years where, for example, supraphysiologic intake of beta carotene can promote certain cancers while an ever increasing number of adverse findings are being linked to mandatory folic acid intake.\textsuperscript{2} To quote Francis Crick (with slight modification), “Almost all aspects of life are engineered at the molecular level, and without understanding molecules, and their interactions, we can only have a very sketchy understanding of life itself.”\textsuperscript{3} With this in mind, we raise the following possible explanations for the findings of Mursu et al.\textsuperscript{1}

- The inverse relationship with calcium and mortality may stem from a reduced ability to synthesize calcitriol from 7-dehydrocholesterol in the skin as we age. Since the main function of vitamin D (calcitriol) is in the control of calcium homeostasis, a reduction in calcitriol may modulate healthy aging.
- Reduced iron need in postmenopausal women should not be ignored, given that excessive iron can act as a free radical generator, with superoxide and hydroxyl radicals causing genomic, protein, and lipid damage associated with cancers and vascular disease. Iron regulation is at the level of acquisition; therefore, given that exfoliation and menstrual losses are the only routes for iron loss, overload can be problematic.
- Humans, as distinct from other species, have extremely low and variable liver dihydrofolate reductase (DHFR) activity. Thus, DHFR may not cope well with even moderate levels of unmetabolized synthetic folic acid, leading to concern that this synthetic analogue may have antimetabolite properties.\textsuperscript{4} It also seems to increase colorectal and other cancer rates,\textsuperscript{5} possibly by a direct effect or via changes to CpG methylation or dTMP metabolism. The negative effect observed by Mursu et al is strongest after fortification!

Are unregulated dietary supplements another failing of nurture over nature? Is the human phenotype being shifted by changing cultural norms; an obesogenic environment confronting thrifty genes;\textsuperscript{6} smaller families, older parents, and increasing in vitro fertilization confronting natural selection by promoting infertility;\textsuperscript{7} and the expanding virtual interface leading to an extended human phenotype (the personal computer/mobile device–dependent sedentary man)? \textsuperscript{8}

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