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Re: Correlating Nutrition to Recent Cancer Mortality Statistics

Wynder and Cohen (1) attribute the declining mortality from breast, prostate, and colon cancers (2) as well as from cardiovascular disease (3) to the reduction of total fat intake in the U.S. population in recent decades. The authors are fully aware of the differential effect of saturated, polyunsaturated, and monounsaturated fat on physiologic parameters and human disease risk—in fact, they have been major scientific contributors in this area. From the perspective of the U.S. population, it may make little difference to focus on total rather than saturated fat, although evidence incriminating saturated fat is strong for prostate cancer but weaker for cardiovascular disease and colorectal cancer and weaker still for breast cancer. The dominance, however, of the English language scientific and general press in the world scene has adversely affected the attitudes toward total fat intake in the Mediterranean countries in which most of the total fat is monounsaturated and is in the form of olive oil (4). There is strong evidence that consumption of olive oil may convey substantial protection against coronary heart disease (5), and several studies have indicated that it may also provide some protection against breast cancer (6) and possibly other forms of cancer (7) and even against osteoporosis (8). Mediterranean countries have lower rates of occurrence of these diseases and conditions in comparison to the United States, even though total fat intake has been as high or higher than that in the United States. The overall evidence points to a beneficial effect of olive oil on human health. Although the data may not be strong enough to dictate substitution of olive oil for other types of lipids in populations who do not traditionally consume it, they strongly suggest that the Mediterranean populations should not risk diverting from their olive oil-centered dietary habits.

Dietary guidelines have been widely perceived as indicating that total fat intake should be reduced. “Total fat,” however, is not a very useful term, because fats and oils are distinct categories in the broad group of lipids. It should be made clear that the evidence for the negative effects of dietary fat, such as it is, does not apply to monounsaturated triglycerides that dominate olive oil.

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References


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Response

Drs. Trichopoulou and Lagiou make a valid and interesting point. Our focus on secular changes in total fat consumption as a possible cause of the recently observed decrease in U.S. cancer mortality rates actually refers to a population (North America) in which olive oil plays a relatively minor role in the diet. Clearly, a unique feature of the Mediterranean diet is its reliance on olive oil, and there is mounting epidemiologic and experimental evidence that olive oil may provide some reduction in the risk of a variety of chronic diseases including heart disease, cancer, diabetes, and perhaps osteoporosis. It should be noted, however, that there are other components of the Mediterranean diet that may also confer protection, such as high consumption of tomatoes, grains, nuts, fruit, and yogurt, as well as a lower consumption of animal fats and vegetable oils, rendering it difficult to single out the effects of olive oil per se. Nonetheless, Drs. Trichopoulou and Lagiou are correct in pointing out that our emphasis on olive oil is a possible cause of the recent drop in U.S. cancer mortality rates may not be generalizable to other countries, particularly those such as Greece and Spain in which olive oil plays a central role in the diet.

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Re: Relationship Between Lifetime Ovaryulatory Cycles and Overexpression of Mutant p53 in Epithelial Ovarian Cancer

Schildkraut et al. (1) recently reported an association between number of lifetime ovulatory cycles and the risk of p53-overexpressed invasive epithelial ovarian cancer, but not of p53-negative cancer. From the data they presented, I conclude exactly the opposite: p53-positive and p53-negative cancers are equally associated with ovulation-related risk factors, the sole exception being age at diagnosis, which was on average some 3 years greater for the p53-positive case subjects. The study participants were all less than 55 years of age at diagnosis/interview; the majority were premenopausal or perimenopausal. Schildkraut et al. estimated the number of lifetime ovulatory cycles from a linear combination of five factors: age at most recent menstrual period (“index age”), age at menarche, and total durations of pregnancies, breastfeeding, and oral contraceptive use. None of the last four mentioned factors differed significantly between the p53-positive and p53-negative case subjects \( P = .71, .14, .06, \text{ and } 0.23, \text{ respectively} \) (1)). Comparing p53-positive and p53-negative cancers, the decreasing odds ratio trends with increasing months pregnant were very close (1), consistent in magnitude with the protective trends seen for parity in many other studies (2,3). Similarly, p53-positive and p53-negative cancers had virtually identical odds ratio trends with duration of oral contraceptive use (1), again of the same magnitude as seen elsewhere (2,3). Age at menarche and duration of breastfeeding contributed very little to the variation in number of ovulatory cycles (1). Thus, only index age is responsible for the purported difference in risk according to lifetime ovulatory cycles.

Furthermore, the authors’ adjustment for continuous age terms need not remove the effect present in the categories of lifetime ovulatory cycles. It is straightforward to show that, even with adjustment for age as a continuous term, age at diagnosis can completely account for the pattern of odds ratios in lifetime ovulatory cycles seen by Schildkraut et al.

While the suggested biologic rationale—that p53 overexpression indicates ovulatory proliferation-induced, p53-related DNA damage (4)—is attractive, the data of Schildkraut et al. provide evidence to the contrary, that p53 overexpression more likely results from damage occurring during neoplastic proliferation of the tumors. They show that, in addition to older age at diagnosis, p53-positive tumors are more likely to be of poorer differentiation than p53-negative tumors \( P<10^{-5} \) and of distant rather than local–regional stage at diagnosis \( P = .0002 \) (1). These well-known features (4–6) thus indicate that p53-positive cancers are those diagnosed later in the neoplastic process, when more genetic errors have accumulated. Therefore, the results do not provide evidence for p53-specific causal mechanisms in the pathogenesis of ovarian cancer.

Finally, Schildkraut et al. (1) state that pregnancy, oral contraceptive use, and lactation all convey their protective effects only through anovulation. However, the number of analyzed case subjects (n = 197) provided insufficient study power to make this conclusion. Ovulation may be involved in the disease process, but it cannot be the entire mechanism (7). Simply put, the reduction in risk with parity [odds ratio = 0.83 for each successive pregnancy (2)] is just too strong compared with the fraction of ovulatory years prevented, at most 5% per pregnancy (i.e., odds ratio = 0.95); these odds ratios are statistically incompatible [two-sided Wald test, \( P<10^{-5} \), using the data summarized by Whittemore et al. (2)] and remain so even accounting for latency (8,9). How “incessant” ovulation is actually involved in ovarian cancer pathogenesis remains a very interesting question, certainly beyond the idea of ovulatory wound repair and accompanying cellular proliferation.

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References

(1) Schildkraut JM, Bastos E, Berchuk A. Relationship between lifetime ovulatory cycles and overexpression of mutant p53 in epithelial...