

**MECHANISMS FOR CANCER PREVENTION BY
CAROTENOIDS: THE ROLE OF THE ANTIOXIDANT
RESPONSE ELEMENT AND THE NRF2 TRANSCRIPTION
FACTOR**

**Joseph Levy, Anat Ben-Dor, Keren Hirsh, Andrea
Skladnik, Michael Danilenko, Micha Steiner, Karin
Linnewiel, and Yoav Sharoni**

Faculty of Health Sciences, Ben-Gurion University of the
Negev and Soroka Medical Center of Kupat Holim, Beer-
Sheva, Israel

The aim of our work is to determine the mechanisms of cancer prevention by carotenoids. Two complementary mechanisms were studied: the induction of phase II detoxification enzymes and inhibition of estradiol signaling in breast and endometrial hormone-dependent cancer in which estrogens are an important risk factor. We found that carotenoids induce phase II enzymes by activation of the antioxidant response element (ARE) and the Nrf2 transcription factor, and that this induction was abolished by dominant negative Nrf2. Unexpectedly, the inhibition of estrogen-induced cancer cell proliferation by carotenoids was also mediated by the activation of Nrf2 through its association with the estrogen transcription complex. Inhibition of estrogen signaling by carotenoids was attenuated by reducing Nrf2 cellular level employing siRNA. Ethanolic extract of lycopene containing unidentified hydrophilic derivatives of the carotenoid activated ARE with a similar potency to lycopene, suggesting that also oxidized derivatives of the carotenoids are effective.