# Women's Higher Risk with N-6 PUFA vs. Men's Relative Advantage: An "N-6 Gender Nutrition Paradox" Hypothesis

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**ABSTRACT:** The "Israeli Paradox" (1996) of low national health rankings despite adequate diet – attributed to high dietary n-6 polyunsaturated fatty acids (PUFA) – coincided with long-observed dichotomies between women's worse international status vs. men's advantage. This raised the possibility of a gender link to high n-6 risk potentially explaining both national phenomena. Israeli women's disadvantage was shown by worse international rankings, i.e., life expectancy (LE) – 11th vs. men's 3rd-best/22 countries (2000), and 14th vs. 6th/34 (2010); and all-cause and all-cancer mortality – both 15th vs. 2nd-best/22 (2000), and 15th vs. 6th/22 and 12th vs. 2nd-best/22 (2010). Cancer mortality rates for breast were 21.8% above vs. prostate 30.4% below Eur-A (27 country) averages (2005). Gender gaps/ratios were smaller than European Union-15 averages, i.e., for LE at birth by 34.4–26.4% (2000–2010), respectively, and at 65 years 45.9–35.3%; all-cause mortality by 43.3–33.4%, and all-cancer 65.2–58.7%. The Israeli diet was mostly close to guidelines, but n-6 intake (10–12% kcal) was much higher than recommended and traditional "Mediterranean diet" levels. Research showing females' greater potential for conversion of PUFA to long-chain PUFA (LCPUFA) may suggest increased production of n-6 eicosanoids with known pro-inflammatory/oxidative/carcinogenic potential. An "Israeli N-6 Gender Nutrition Paradox" hypothesis is suggested here for the first time, associating women's higher risk and lead in the national "paradox" with greater potential for n-6 conversion to pro-inflammatory/oxidative/carcinogenic eicosanoids compared to men. This may also exacerbate women's risk associated with genetic predisposition (i.e., *BRCA*) and/or sociopolitical stress. Global abandonment of traditional diets/foods together with increasing n-6 consumption and western disease rates emphasize the importance of considering gender nutrition in epidemiology and preventive strategies.

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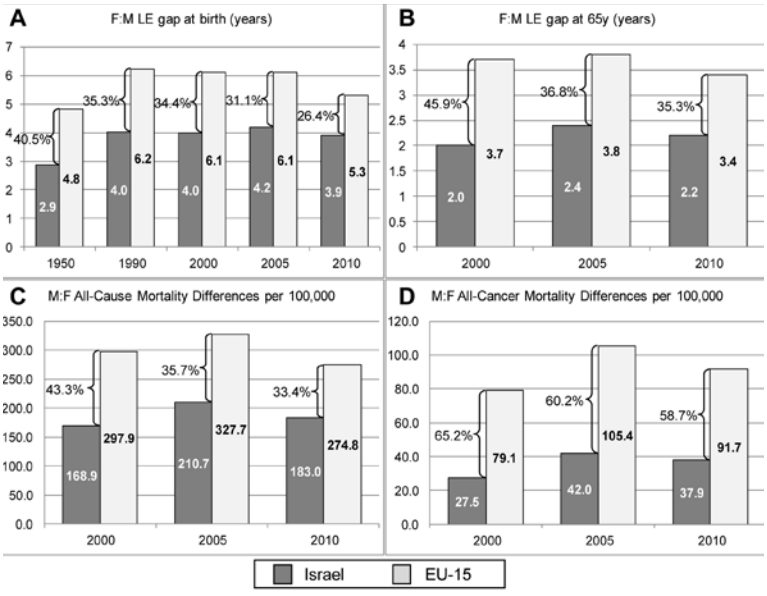
**KEY WORDS:** cancer, diet, gender, n-6/n-3, polyunsaturated fatty acids (PUFA), women

The "Israeli Paradox" (1996) described unexpectedly worse international health rankings, despite a diet close to guidelines, with a higher prevalence of cancer, cardiovascular and metabolic diseases than in other Mediterranean countries (i.e., Greece, Italy, Spain), and comparable to western countries (United States and Northern Europe) [1,2]. This discrepancy was attributed to a very high n-6 polyunsaturated fatty acid intake, mostly linoleic acid (18:2), ≈12% of energy intake (kcal) [1], and ≈26% fatty acids in adipose tissue [1,3]. The "paradox" refers to the unexpected negative effects of high dietary n-6, which could be associated with increased production of arachidonic acid (20:4) and related eicosanoids/prostaglandins with high pro-inflammatory/oxidative/carcinogenic potential [4]. This is despite LA being a nutritionally essential FA with known positive effects on lipidemia and cardiovascular disease.

Epidemiological/demographic research studies have long shown Israeli women to have lower health rankings compared to women in other countries, and relative to Israeli men, who fare better than their counterparts [5]. Women's relative disadvantage is further expressed by very small male-female gaps, i.e., in life expectancy – both at birth, which includes early-life risks, and at 65 years, which expresses mainly differences in chronic disease. This was initially attributed to immigration stress, later to higher prevalence of *BRCA* gene mutations in Ashkenazi women, in approximately 2.5% vs. up to 1% of non-Jews and non-Ashkenazi Jews [6], and recently to immigrants' imported traditional gender ratios [5]. Although a recent national population-based study found similar breast cancer mortality rates in carriers and non-carriers of a BRCA *muta*tion [7], increased penetration of breast cancer among *BRCA*1/2-positive Jews born after 1940 [8,9] concurrent with the "industrial food revolution" [9] could also support the nutritional hypothesis. This is in contrast with the apparent protective effect of traditional diets – such as the "Mediterranean" diet, known to be higher in n-9 monounsaturated FA and n-3 PUFA – against western diseases [10].

**Figure 1.** Gender differences in life expectancy (LE) and mortality, Israeli women and men compared to group averages of western countries (1950–1990*, 2000–2010**). **[A]** Female:male gap at birth, **[B]** Female:male gap at age 65, **[C]** Male:female all-cause mortality differences per 100/000, **[D]** Male:female all-cancer mortality differences per 100/000




*1950–1990 data based on Staetsky and Hinde (2009) [5]

**2000–2010 data based on WHO-HFA presented by the Israel Ministry of Health [2,11]

## GENDER DIFFERENCES IN LIFE EXPECTANCY AND DISEASE RISK

Since the 1950s, Israeli gender differentials in LE have been very low when compared to other developed countries, reflecting women's relatively low and men's high LE. Israeli male:female LE differences were much smaller than the averages of 18 western countries in the 1950s–1990s (by 25.4–39.6%, respectively) [Figure 1] [5]; the smallest among Eur-A countries with low mortality rates and well below the Eur-A average from 1980 to 2000 [Figure 2A]; the smallest among 22 developed countries in 2000 [Figure 3A]; and much smaller in 2000–2010 (by 39.5–25.4%) compared to 15 European Union countries with similar socioeconomic status (EU-15) [Table 1 and Figure 1] [2,11]. Where the LE of Israeli women was similar to/slightly shorter than the EU-15 average, men's LE was among the longest [12]; where women's mortality rates in 2000–2010 were slightly higher (by 2.1–5.9%), men's mortality was much lower (by 16.5–9.0%), and resultant male-female mortality ratios were also much lower (by 43.3–33.4%, respectively) [2] [Table 1 and Figure 1C and D].

CVD was initially assumed to be the leading cause of Israeli women's health disadvantage [13] and, correspondingly, male:female CVD mortality ratios were among the smallest in international comparisons. However, the gender ratios for cancer rates were even smaller, and thus contributed significantly more than CVD to Israeli's exceedingly small male-female LE ratio from the 1950s to 1990s [5]. This was shown (2000) by smaller male:female mortality ratio for cancer (1.23) than for all-cause (1.38), and much smaller (by 67.1%) than for ischemic heart disease (1.70) [Figure 3B]. In 2000–2010, Israeli male-female mortality differences for all-cancer were smaller than for all-cause [Table 1, Figure 1], and both were smaller than the EU-15 average (all-cancer smaller by 62–58.7% and all-cause by 43.3–33.4%). This showed that the smaller gender ratio for cancer was consistently more contributory than other diseases to the characteristically small gender gap among Israelis.

Women's disadvantage in cancer mortality was shown by higher rates relative to other countries [1,5], i.e., 21.8% higher than Eur-A (2005) and compared to the EU-15 average (by 8.0–3.6%, 2000–2010) [Table 1]; in their lead in the national "cancer-shift" over heart disease mortality [14]; and by consistently worse international cancer mortality rankings vs. men's advantage, i.e., 15th vs. 37th in 44 Eurasian countries (1999); 17th vs. 34th in 37 European countries (2005); 15th vs. men's 2nd-best in 22 developed countries (2005) [2], and 23rd vs. men's 5th-best in 30 countries with the world's highest LE (2006) [15].

Men's advantage in cancer risk was emphasized by lower disease mortality rates compared to 18 western countries (1950–1990) [5], compared to the Eur-A average (1970–1992) [Figures 2B and 2C] [16], and by men's lower all-cancer mortality rates than the EU-15 average (by 22.4–27.9%) [Table 1, 2000–2010]. Moreover, prostate cancer mortality was much lower than the Eur-A average (-30.4%), where breast cancer rates were much higher (+21.8%) (2005). The resultant Israeli prostate:breast cancer mortality ratio (0.55:1) was 56.1% lower than the EU-15 average (0.98:1) [2] [Figure 3B] and lower compared to similarly developed Mediterranean countries such as Greece (0.72:1), France (0.92:1), Spain (0.93:1) and Italy (1.56:1) [11]. Within Israel, men's all-cancer rates were slightly lower than women's [17,18], with prostate cancer incidence, 8.2%, about half that of breast, 17.1%, and mortality 4.9% vs. 10.8% [2], contributing 9.8% of men's and 21.3% of women's mortality (2000) [12]; in 2005, the incidence was 9.6% vs. 15.9%, mortality 4.2% vs. 10.1%, contributing 19.7% vs. 30.8% of total mortality. Taken together, it appears that both women's worse and men's better rates contributed to Israel's characteristically small gender gap. However, this trend declined from the 1950s to 2010 [Figure 1], along with a relative decrease in the male advantage [Table 1], i.e., in LE and all-cause mortality, though Israeli men's cancer rates continued to be lower relative to other countries.

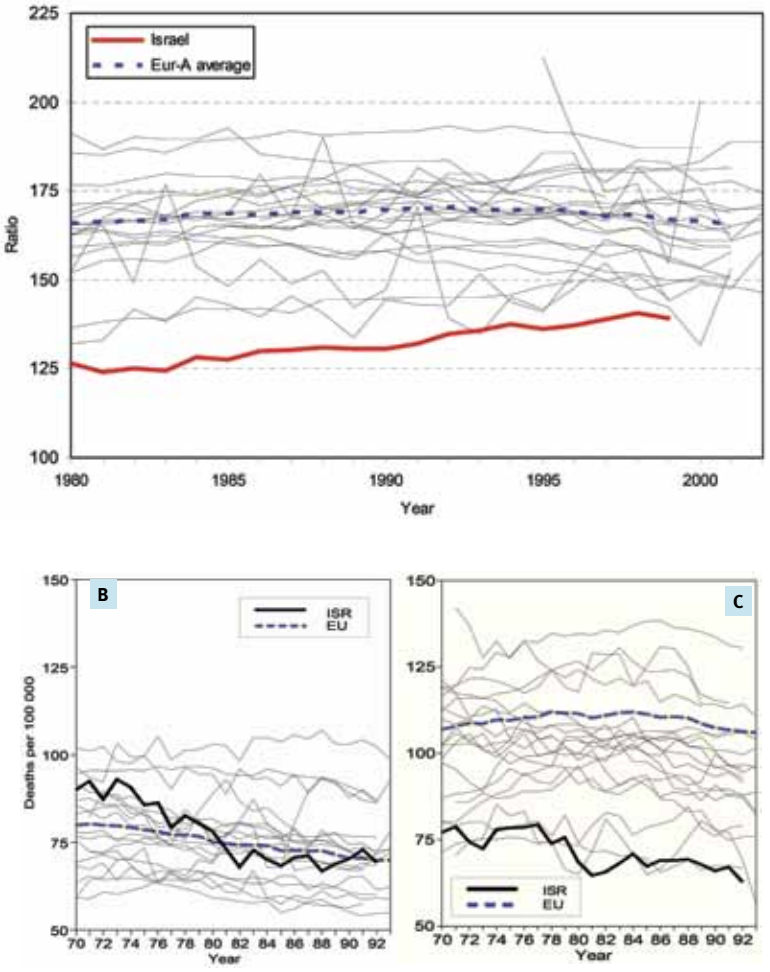
## DIETARY N-6 INTAKE PATTERNS

The Israeli diet is mostly compatible with recommendations in both women and men, i.e., for energy (women-men 1533–2212 kcal/day), protein (58.0–86.0 g/day, 15.1–15.6% kcal), carbohydrates (203.0–282.0 g/day, 53.0–51.0% kcal), fiber (15.0–19.0 g/day, 25.9–22.1% carbohydrates), total fat (57.0–84.0 g/day, 33.5–34.2% kcal), saturated FA (16.4–23.3 g/day, 4.3–4.2% kcal), n-9 (18.8–28.8 g/day, 4.9–5.2% kcal, mostly oleic acid [18:1] from canola/olive oils), and n-3 (1.5–2.2 g/day, 0.9% kcal, mostly alpha-linolenic acid [18:3] from nuts, seeds, and canola oil) [19]. However, n-6 was exceedingly high ≈12% kcal (from soy/corn oils) [1], associated with very high adipose LA accumulation, ≈26% FA (1996). Later reports suggested a decline in n-6 intake to 10%kcal, with 25% of the population still consuming LA at ≥ 12%kcal [3], and a national report (2001) showed n-6 intake of 8.4% kcal (15.6 g/day) in men and women [19]. The decline in n-6 intake can be attributed to increasing intakes of low-n-6 canola oil (with ≈19% LA) and olive oil (≈10% LA) [20], which partially replaced the high-n-6 soy (≈51% LA) and corn (≈55% LA) oils that had dominated since the 1950s. However, dietary n-6 levels and n-6:n-3 ratios have remained ≈twofold higher than the level and ratio in the traditional Mediterranean diet (7.8 g/day and 4.3:1) [19,21] – twice the maximal safe and effective intake (≈3.8% kcal) for incorporation into tissue lipids [22]. It is also much higher than official recommendations, i.e., by Health and Welfare Canada, U.S. Institute of Medicine, British Nutrition Foundation, and French Apports Nutritionnels Conseillés. Recent n-6 recommendations of 5–10%kcal by the American Heart Association raised critical response arguing that these levels were shown to be associated with increased risk [23].

## N-6 AND DISEASE RISK

High intakes of n-6 (mostly LA) with increased ARA and related pro-inflammatory/oxidative/carcinogenic eicosanoids [24] were found to be associated with oxidation of low density lipoproteins and adipose tissue lipids [25], and greater risk of myocardial infarction [3], chronic inflammatory diseases [24] and breast cancer [26]. Recent epidemiologic research incorporating large cohorts has suggested a positive association between n-6 intake and risk of breast cancer, and negative association with n-3 ALA and n-9 OA [27]. High n-6 was also associated with estrogen-driven upregulation of oncogenes (the *BRCA*1 gene), whereas inhibitors of eicosanoid/prostaglandin formation (salicylic acid) decreased *BRCA*1 mRNA expression and attenuated breast cancer cell proliferation [28].

**Figure 2.** Gender differences in mortality, Israel and Eur-A* [12,16]. **[A]** Male:female total mortality ratio (1980–2000), **[B]** All-cancer mortality, males ‹ 64 years old, Israel and Eur-A (1970–92), **[C]** All-cancer mortality, females ‹ 64 years old, Israel and Eur-A (1970–92)

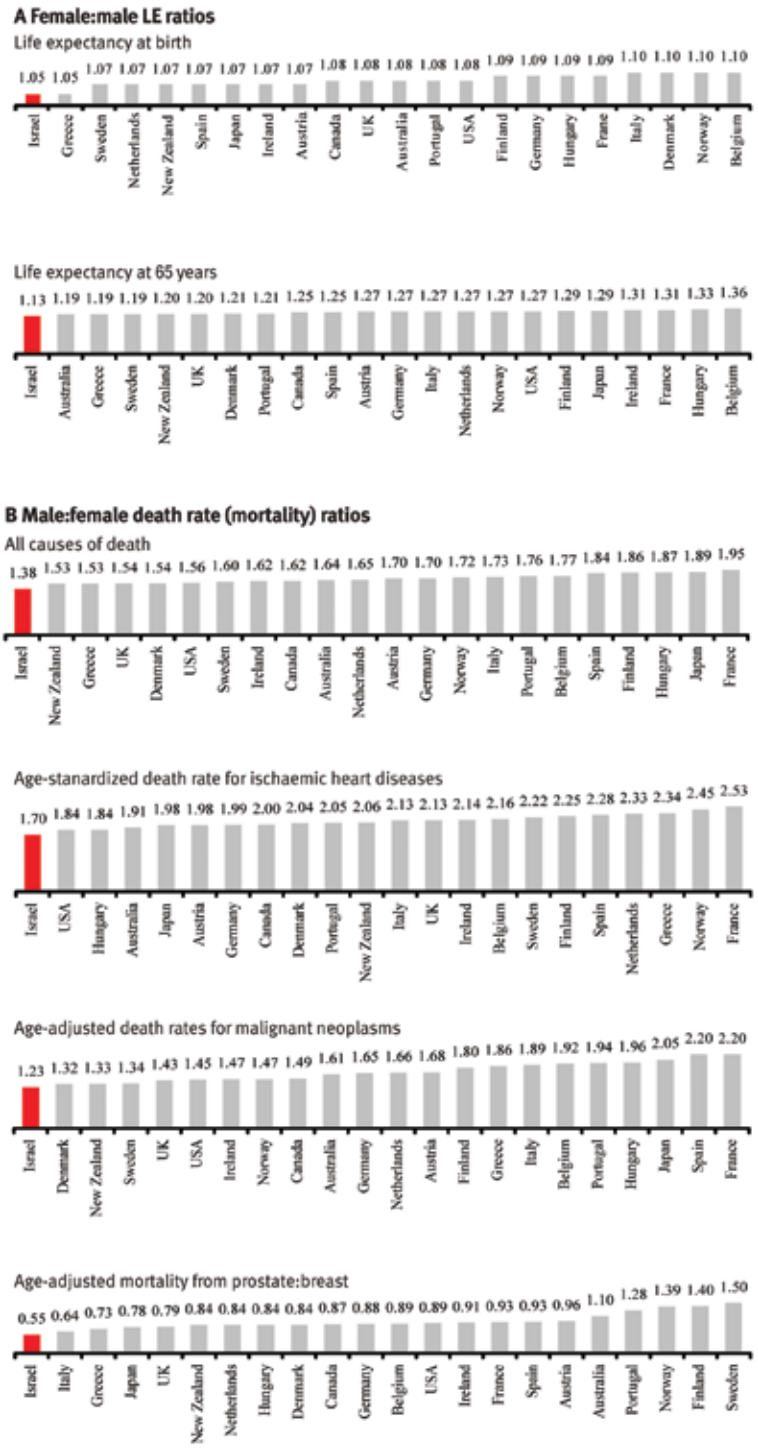



* Eur-A (27 countries with very low child and adult mortality rates) = Andorra, Austria, Belgium, Croatia, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, and the UK

## EPIDEMIOLOGICAL SUPPORT FOR N-6-ASSOCIATED RISK

The lifelong cancer risk of Israeli Jewish women was twice that of Israeli Arab women, 1:3 vs. 1:6 (2000) [18], and their breast cancer incidence ranked 3rd highest vs. Israeli Arab women who ranked 3rd lowest/18 countries (1997). This was concurrent with a higher Jewish dietary n-6 (by 25.5%) and n-6:n-9 ratio (by 40.3%) [19] compared to Israeli Arabs,

**Figure 3.** Gender differences in life expectancy (LE), disease, and mortality ratios, Israel among countries with comparable health care systems and economic status (2000) [11]. **[A]** Female:male LE ratios, **[B]** Male:female mortality ratios




and higher than other Mediterranean and neighboring Arab countries [10,19,20]. However, all-cancer mortality rates increased much more rapidly in Israeli Arabs compared to Israeli Jews (1982–2002), ≈twofold in men and ≈eightfold in women, with a breast cancer increase of ≈eightfold, gradually narrowing the gap between the two population groups [17]. This was concurrent with increased n-6 intake, as soy and corn oils partially replaced Arabs' traditionally dominant high-n-9 olive oil [20].

Several European countries were found to have high n-6 intakes close to recent (reduced) Israeli levels (12.3–16.1 g/day) [20], with high female breast cancer rates and evidence of positive correlations to dietary n-6 and n-6:n-3 long-chain PUFA ratios, and negative correlations to n-3 LCPUFA [27,29]. The U.S., whose breast cancer rates are the highest in the world (incidence 101.1/100,000, mortality 19.0/100,000) [29], has average dietary n-6 intakes of 15.6 g/day and n-6:n-3 ratio of approximately 9:1 [30], both similar to recent Israeli values. A U.S. multi-ethnic case-control study showed an association between breast cancer incidence and use of high n-6 vegetable/corn oils relative to olive/canola oils rich in n-9 [31]. In Singapore, which has the highest breast cancer incidence in Asia (54.9/100,000), risk has increased with adoption of a western diet, including increased n-6 intake and n-6:n-3 ratio [32]. Among Alaskan Natives (1990–2005), women's breast cancer incidence increased by 46.4% (from 66.4 to 97.2/100.000) while men's prostate cancer decreased by 29.3% (98.4 to 69.5/100.000) [33] with abandonment of the Native Alaskan diet, traditionally high in n-3 [34].

High n-6 LA and ARA content of adipose tissue (i.e., in breast tissue), an accepted measure of intake, has been associated with increased breast cancer risk in case-control studies, while low adipose n-6:n-3 ratio and high n-3 LCPUFA eicosapentaenoic acid and docosahexaenoic acid content showed a protective effect [27]. The above epidemiologic findings appear to support the n-6 gender nutrition hypothesis, with Israel representing an extreme case.

## GENDER DIFFERENCES IN FATTY ACID METABOLISM AND PATHOPHYSIOLOGY

Gender-mediated differences in FA metabolism have been suggested by several researchers, in both animal models and humans. In vivo studies have shown that testosterone reduces the activities of delta-5- and delta-6-desaturases, key enzymes in the conversion of PUFA to LCPUFA, i.e., n-6 LA to ARA, and n-3 ALA to EPA and DHA, while estrogen was associated with an increase [35]. Activities of delta-5 and delta-6-desaturase enzymes were 1.2- to 3-fold greater in females compared to males in a rat liver model, with mRNA expression greater by 3.8- and 2.5-fold, respectively [36]. This is further evidenced by lower male ratios

**Table 1.** Life expectancy and mortality rates, Israeli women and men and the EU-15* averages (2000–2010)

| | 2000 | | | 2005 | | | 2010 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Israel | EU-15 | % Diff | Israel | EU-15 | % Diff | Israel | EU-15 | % Diff |
| **Females** | | | | | | | | | |
| LE at birth (yrs) | 80.0 | 79.9 | +0.1% | 81.8 | 82.0 | -0.2% | 83.0 | 82.9 | +0.1% |
| LE at 65 (yrs) | 18.0 | 18.6 | -3.2% | 19.8 | 20.3 | -2.5% | 20.7 | 20.9 | -1.0% |
| All-cause mortality per 100,000 | 439.1 | 430.1 | +2.1% | 512.1 | 498.6 | +2.7% | 477.6 | 451.1 | +5.9% |
| All-cancer mortality per 100,000 | 120.8 | 111.9 | +8.0% | 145.3 | 137.0 | +6.1% | 133.4 | 128.8 | +3.6% |
| **Males** | | | | | | | | | |
| LE at birth (yrs) | 76.0 | 73.8 | +3.0% | 77.6 | 75.9 | +2.2% | 79.1 | 77.6 | +1.9% |
| LE at age 65 (yrs) | 16.0 | 14.9 | +7.4% | 17.4 | 16.5 | +5.5% | 18.5 | 17.5 | +5.7% |
| All-cause mortality per 100,000 | 608.0 | 728.0 | -16.5% | 722.8 | 826.3 | -12.5% | 660.6 | 725.9 | -9.0% |
| All-cancer mortality per 100,000 | 148.3 | 191.0 | -22.4% | 187.3 | 242.4 | -22.7% | 171.3 | 220.5 | -22.3% |

LE = life expectancy, EU = European Union
*Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom

of ARA:LA and DHA:ALA compared to females, in both plasma and cellular fractions [35].

In clinical evaluations, women were found to have greater or more efficient PUFA conversions compared to men [37,38], and dietary N-6 LA-induced increases in promutagenic DNA etheno-adducts in white blood cells, by up to 40-fold, while no significant change was observed in men [39]. Carcinogenic/mutagenic byproducts of n-6 prostaglandins and peroxidation, such as malonaldehyde, have also been suggested to affect women more than men [40].

**Epidemiological comparisons suggest an Israeli gender dichotomy unfavorable to women vs. men's relative advantage – particularly shown in cancer – with a resultant international lead in small gender differences in life expenctany and mortality rates**

## SUMMARY

An "N-6 Gender Nutrition Paradox" hypothesis of women's higher health risk with increased n-6 intake, compared to men's relative advantage, is suggested here to be associated with women's greater capacity for conversion of n-6 PUFA to LCPUFA, i.e., LA to ARA, and related pro-inflammatory/oxidative/carcinogenic eicosanoids. This suggests a biological gender-based explanation for the "Israeli paradox" of the unexpectedly low national health status despite an otherwise adequate diet, and for women's long-observed relative disadvantage. These findings support the Israeli paradox hypothesis and introduce the "n-6 gender nutrition" aspect, suggesting a redefinition – namely, an Israeli "N-6 Gender Nutrition Paradox" hypothesis.

**High female potential for PUFA conversion to LCPUFA and resultant pro-inflammatory/carcinogenic eicosanoids may increase women's sensitivity to high n-6 intake, as compared to men**

With declining n-6 and increasing n-3 and n-9 intakes, i.e., from canola and olive oils substituting for high n-6 LA corn and soy oils, the gender discrepancies have been decreasing. However, a reverse dietary trend among Israeli Arabs has reproduced the phenomenon of women's increased risk with n-6 intake. These findings, together with additional epidemiologic evidence of the link between n-6 and western diseases – especially cancer – may support the n-6 gender nutrition hypothesis, presented here for the first time. The link may not preclude, but could potentially exacerbate, risks associated with other etiologies, i.e. *BCRA*1/2 mutations.

Limitations of this analysis may have been the use of official statistics produced for other purposes, the observational nature of available studies and inability to adjust for all possible confounders, the small scale of nutritional studies, and a population with transitional, immigration and sociopolitical stresses as well as highly diverse traditions.

Given the global abandonment of protective traditional diets and increase in n-6 consumption concurrent with western diseases, this specific aspect – and gender nutrition in general – warrants research within the new framework of genetic/epigenetic and personalized medicine concepts.

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**ABBREVIATIONS**

A glossary of the abbreviations appears at the end of the article

**ALA** alpha-linolenic acid, 18:3 n-3
**ARA** arachidonic acid, 20:4 n-6
***BRCA*** breast cancer gene mutation
**CDC** Centers for Disease Control
**CVD** cardiovascular disease
**DHA** docosahexaenoic acid, 22:6 n-3
**DNA** deoxyribonucleic acid
**EPA** eicosapentaenoic acid, 20:5 n-3
**EU** European Union
**EU-15** 15 selected European Union countries
**Eur-A** 27 European countries with low mortality rates
**FA** fatty acid
**LA** linoleic acid, 18:2 n-6
**LCPUFA** long-chain polyunsaturated fatty acid
**LE** life expectancy
**mRNA** messenger ribonucleic acid
**MUFA** monounsaturated fatty acid
**n-** omega- (n)3, 6, 9 fatty acids
**OA** oleic acid, 18:1 n-9
**PUFA** polyunsaturated fatty acid
**SFA** saturated fatty acid

## Capsule

### Commensal microflora help to regulate the numbers and functions of natural killer T (NKT) cells in the colon and lung in mice

Epidemiological studies have suggested that the increase in the incidence of asthma and other inflammatory diseases seen in many parts of the world may be due to a reduced exposure to microbes during early childhood. Olszak and co-workers show that commensal microflora help to regulate the numbers and functions of natural killer T (NKT) cells in the colon and lung in mice. Germ-free mice had elevated numbers of NKT cells in these tissues and were more susceptible to chemically induced colitis and allergic asthma. Neonatal recolonization of germ-free mice with microflora prevented enhanced colitis and asthma sensitivity; however, exposure of adult mice to these conditions was not effective. Thus, early exposure to microbes has important, lasting effects on the immune system's sensitivity to inflammation.

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Eitan Israeli

## Capsule

### B cell receptor signal transduction in the GC is short-circuited by high phosphatase activity

Germinal centers (GCs) generate memory B and plasma cells, which are essential for long-lived humoral immunity. GC B cells with high affinity B cell receptors (BCRs) are selectively expanded. To enable this selection, BCRs of such cells are thought to signal differently from those with lower affinity. Khalil et al. show that, surprisingly, most proliferating GC B cells did not demonstrate active BCR signaling. Rather, spontaneous and induced signaling was limited by increased phosphatase activity. Accordingly, both SH2 domain-containing phosphatase-1 (SHP-1) and SH2 domain-containing inositol 5 phosphatase were hyperphosphorylated in GC cells and remained co-localized with BCRs after ligation. Furthermore, SHP-1 was required for GC maintenance. Intriguingly, GC B cells in the cell cycle $G_2$ period regained responsiveness to BCR stimulation. These data have implications for how higher affinity B cells are selected in the GC.

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Eitan Israeli

**Every human being's essential nature is perfect and faultless, but after years of immersion in the world we easily forget our roots and take on a counterfeit nature**

Lao-Tzu (6th century BCE), Chinese philosopher