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Fighting Cancer: Can Soy Be of Benefit?

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In This Issue

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ROLE OF SOY IN THE PREVENTION, TREATMENT OF SIX CANCER TYPES

By Mark Messina, PhD, MS

Since the early 1990s soyfoods have been widely investigated for their potential role in cancer prevention.[1] Much of this research has been conducted because soyfoods are uniquely-rich sources of isoflavones. Most of the cancer research involving soy has focused on breast and prostate cancer because these cancers are known to be hormonally regulated and countries that consume soyfoods have low incidence rates of both cancers.[2] Previous issues of this newsletter have addressed these two cancers and the reader is referred to the references for additional information on breast[3-7] and prostate[8-10] cancer.

The etiology of a number of cancers is thought to include a hormonal component and isoflavones potentially inhibit carcinogenesis through both hormonal and non-hormonal mechanisms.[11] In fact, initial interest in the chemopreventive effects of isoflavones was based on the ability of genistein to inhibit the activity of an enzyme overexpressed in cancer cells.[12] Therefore, soy may impact the development of several cancers, not just breast and prostate cancer. This article provides a brief overview based primarily on the clinical and epidemiologic research of the current understanding of soy intake and risk of cancers of the endometrium, colon and rectum, lung, bladder, skin and thyroid.

Endometrial Cancer (EC)

Endometrial cancer (cancer of the corpus uteri) represents the most common gynecological malignancy in the industrialized world and is the seventh most common cancer among females (although incidence and mortality rates vary markedly among geographical regions and countries).[2] The highest rates of this cancer are in the United States and Europe and the lowest are in Asia and Africa.[13]

Several observations support the important role that estrogen plays in the etiology of EC[14] although the extent to which this is true may be influenced by estrogen receptor (ER) polymorphisms.[15] "Ever users" of unopposed estrogen therapy are about two to three times more likely to develop EC as "never users"[16-18] and women with EC have increased ovarian volume and higher estradiol levels.[19] For this reason, soyfoods could be theorized to increase or decrease EC risk because they contain isoflavones.

Two recently published meta-analyses of the epidemiologic data have evaluated the relationship between soy intake and EC risk. One such analysis involving ten studies (eight case-control, two prospective) found soy intake was inversely associated with EC risk with an overall risk estimate (RE) of 0.81 (95% confidence interval [CI]: 0.72, 0.91).[20] Subgroup analyses revealed statistically significant protective effects for both Asian (RE=0.79, 95% CI: 0.66, 0.95) and non-Asian (RE=0.83, 95% CI: 0.71, 0.96) populations.

The second analysis also found soy (isoflavone) intake was protective against EC (odds ratio [OR]=0.81, 95% CI: 0.74, 0.89) but sub-analysis indicated reduced risks were limited to the ten case-control studies (OR 0.81: 95% CI: 0.73, 0.90). Nevertheless, there were only three cohort studies in the analysis and the reduction in risk was close to significant.[21] Dietary isoflavones were associated with protection against EC in both Asian and non-Asian countries.

Clinical studies indicate that unlike estrogen, isoflavones do not adversely affect the endometrium. This conclusion is based on a review by the European Food Safety Authority of 25 clinical studies that measured endometrial thickness and nine that measured histopathological changes in the endometrium.[22] Interestingly, a recently published meta-analysis found that when all clinical studies (N=23; 2,167 participants) were included in the analysis, there was no effect of isoflavones on endometrial thickness, whereas there was a significant (P=0.04) decrease in thickness when considering only the seven North American trials which involved 726 women.[23]

On the other hand, there was a small increase in thickness among women involved in the three Asian trials, but none of these studies actually intervened with isoflavones derived from soybeans.

Finally, Bitto et al.[24] found in a six-month trial involving 56 premenopausal women with non-atypical endometrial hyperplasia that the isoflavone genistein (54 mg/day) significantly improved symptoms in comparison to a placebo and had a similar effect as norethisterone acetate (a progestin used to treat hyperplasia). These results suggest genistein was functioning as an anti-estrogen possibly by upregulating ERβ expression. The daily amount of genistein taken by the women in this study is provided by ~4 servings of soyfoods.

Colorectal Cancer (CRC)

Colorectal cancer is the third most prevalent cancer worldwide and one of the most common solid carcinomas in Western countries.[25] CRC incidence rates are higher in developed nations than in developing countries.[26]

A meta-analysis of 17 epidemiologic studies, which consisted of 13 case-control and four prospective cohort studies, showed that soy isoflavone consumption was associated with a reduction in CRC risk (relative risk [RR]=0.78, 95% CI: 0.72, 0.85). However, subgroup analysis indicated a protective effect was observed only in Asian populations (RR=0.79; 95% CI: 0.72-0.87), and in case-control studies (RR=0.76; 95% CI: 0.68–0.84).[27] The lack of effect in non-Asian studies is not surprising because, as pointed out more than a decade ago, typical Western isoflavone intake is likely too low to exert physiological effects.[28]

A 2016 meta-analysis concurs with the aforementioned meta-analysis in finding a non-significant decreased risk of CRC associated with isoflavones among prospective studies (RR=0.94, 95% CI: 0.83, 1.07) whereas the association was significant among case-control studies for total isoflavone intake (RR=0.86; 95% CI: 0.77, 0.96).[29]

Theoretically, isoflavones could reduce CRC risk because they preferentially bind to ERβ in comparison to ERα;[30] targeting ERβ has been suggested as being a novel clinical approach for management of colorectal adenomatous polyps and prevention of colorectal carcinoma in patients at risk for this disease.[31] However, a 12-month trial comparing the effects of 58 g/day soy protein containing either 3 or 83 mg isoflavones found the isoflavone-rich protein did not reduce colorectal epithelial cell proliferation or the average height of proliferating cells in the cecum, sigmoid colon, and rectum and actually increased cell proliferation measures in the sigmoid colon.[32]

Lung Cancer (LC)

Smoking contributes to 80% and 90% of lung cancer (LC) deaths in women and men, respectively. Men who smoke are 23 times more, and women who smoke are 13 times more likely to develop LC than those who have never smoked.[33] Nevertheless, there still appears to be a role for lifestyle in the etiology of LC.

A meta-analysis of 11 epidemiologic studies found an inverse association between soy protein intake and risk of LC that was of borderline statistical significance (OR=0.98, 95% CI: 0.96, 1.00). Sub-analysis indicated the inverse association was statistically significant in non-smokers (OR=0.96; 95% CI: 0.93, 0.99) and stronger than in smokers (P for difference <0.05).[34] The findings did not differ according to gender, study design or types of soyfoods consumed. Soy protein was used as a common measure of soy intake in this analysis.

Similar results were reported for a meta-analysis of eight prospective and seven case-control studies wherein isoflavones were associated with a significantly decreased risk of LC in both prospective and case-control studies; however, sub-analysis indicated isoflavones were associated with a decreased risk of LC among never smokers (5 datasets from 4 studies, RR=0.64, 95% CI: 0.51, 0.79) but not among former/current smokers (4 datasets from 3 studies, RR=1.03, 95% CI: 0.86, 1.24).[29]

No clinical studies relevant to LC were identified, but in animal models of LC, the administration of isoflavones significantly decreases tumor incidence and increases the life span of the tumor-bearing animals,[35] particularly in female mice.[36] Emerging evidence suggests that estrogen signaling promotes LC progression and ER antagonists such as tamoxifen may counteract the detrimental effect of hormone therapy on LC.[37] Therefore, although very speculative, the proposed protective effects of soy against LC could result from isoflavones exerting an anti-estrogenic effect. On the other hand, it is recognized that the molecular profile of tumors from smokers differs from non-smokers with the latter being more likely to have mutations of the epidermal growth factor receptor,[38] an oncogene which may be suppressed by the isoflavone genistein.[39] Finally, a mouse study reported that soy isoflavones given pre- and post-radiation protect the lungs against the adverse effects of radiation treatment for LC.[40]

Bladder Cancer (BC)

Bladder cancer is one of the most common malignancies affecting the urinary system. It is the third most common male and tenth most common female cancer in the United States.[41] In comparison, the incidence of bladder cancer in Asia is relatively low.[42-43] Nevertheless, two Chinese prospective studies raised the possibility that soy could increase risk of BC.

Continued on pg. 4

The Shanghai Cohort Study reported that, compared to men consuming soy less than once a week, the RR (95% CI) for those who consumed soy 1–<3 times per week, 3–<7 times a week and daily were 2.05 (0.80, 5.29), 2.45 (0.89, 6.76) and 4.61 (1.57, 13.51), respectively (P for trend=0.004) after controlling for a number of potential confounders. The study involved 18,244 men aged 45–64 years who were followed for as long as 16 years.[44] Similar results were reported in the Singapore Chinese Health Study. Relative to the lowest quartile of energy-adjusted total soy intake (<36.9 g/1000 Kcal), the highest quartile of total soy intake (≥92.5 g/1000 Kcal) was associated with a 2.3-fold increase in bladder cancer risk (95% CI: 1.1, 5.1) after adjustment for potential confounders.[45] However, in contrast, a meta-analysis that included these two studies, two additional prospective studies and one case-control study, found no relationship between BC risk and isoflavone intake, although the increased risk was close to significant.[29]

In contrast to the epidemiologic data, Zhou et al.[46,47] reported that soybean isoflavones and soy phytochemical concentrates inhibit the growth of murine and human bladder cell lines in vitro and in vivo in a dose-dependent manner, and Wang et al.[48] showed that genistein enhanced the efficacy of a commonly used drug to treat bladder cancer in mice.

Finally, a phase two randomized, placebo-controlled trial by Messing et al.[39] found that genistein administration for 14 to 21 days before surgery decreased phosphorylation of epidermal growth factor receptor in bladder tumors, suggesting that this isoflavone could inhibit one aspect of the carcinogenesis pathway. However, because a pharmacological dose (300 mg/day) of genistein was used, the findings from this trial may not be applicable to the consumption of soyfoods.

Skin Cancer (Melanoma)

Only very limited preclinical research involving isoflavones and melanoma has been conducted, but there is a theoretical basis for speculating that these soybean constituents reduce risk of skin cancer.

Melanoma incidence is higher in males than in females and females have a significant survival advantage over men. ERβ is the predominant ER in melanoma and its expression decreases in melanoma progression which supports its role as a tumor suppressor.[49] For this reason, ERβ is now considered an effective molecular target for melanoma treatment, and ERβ agonists are proposed as effective in helping to prevent and/or treat melanoma.[49] As noted previously, isoflavones preferentially bind to and activate ERβ in comparison to ERα.[30]

A study with mice implanted with melanoma cells showed that genistein (15 mg/kg body weight) decreased tumor volume and weight by approximately 30% and reduced the quantity of melanin (and the degree of erythema) in direct proportion to the number of days of treatment. Furthermore, no metastasis to the liver was recorded in the treated group whereas, significant metastasis occurred in the control mice.[50] While these findings are impressive, their relevance to humans consuming soyfoods is very unclear given the large dose of genistein employed and the fact that it was administered by intraperitoneal injection.

A second mouse study, which may be more relevant, compared the effects of isolated soy protein (ISP) and selenium-enriched ISP with a casein-containing diet on pulmonary metastasis of murine melanoma cells. Mice were fed their respective diets for two weeks before and two weeks after injection of the cancer cells. In comparison to mice fed casein, the number of mice with ≥50 tumors was significantly decreased in animals fed soy protein, and the exposure to selenium further enhanced tumor suppression.[51]

Thyroid Cancer

The suggestion has been made that soy intake may increase thyroid cancer risk, perhaps by increasing serum levels of thyroid stimulating hormone (TSH).[52-54] However, the clinical evidence shows conclusively that neither soy nor isoflavones increase TSH levels in people with normal-functioning thyroids.[55,56] Furthermore, although Kimura et al.[57] found that the addition of soy to iodine-deficient diets increased malignant goiter in Wistar rats, Son et al.[58,59] found no effect of isoflavones on thyroid carcinogenesis in male[58] and female[59] rats. Furthermore, Seike et al.[60] found that dietary genistein inhibited chemically-induced thyroid cancer.

Epidemiologic data reported by Takezaki et al.[61] found that soy intake was unrelated to thyroid cancer risk among Japanese women in Nagoya. Furthermore, a U.S. case-control study by Horn-Ross et al.[62] found that isoflavone intake was inversely related to risk of thyroid cancer. Also, although thyroid cancer incidence rates are higher among Southeast Asians living in the United States in comparison to other ethnic groups, low soy/isoflavone intake was identified as contributing to these higher rates.[63]

Summary and Conclusions

Definitively establishing diet/cancer relationships is extremely difficult. Understanding of these relationships is based primarily on cohort studies. Intermediary markers for cancer are less well established then they are for other chronic diseases such as heart disease (blood pressure, LDL-cholesterol) and osteoporosis (bone mineral density). Consequently, clinical studies focused on intermediary markers for cancer are generally less revealing than they are for other chronic diseases. Although animal studies are widely used in cancer research, they often fall short of being able to predict human responses.[64,65]

Of the cancers addressed above, the epidemiologic data are most supportive of a protective effect of soy against EC and CRC although this support is based primarily on case-control rather than cohort stud-

ies. For a variety of reasons, case-control studies carry less weight within the epidemiologic community than cohort studies. Although there is a theoretical basis for soy reducing risk of these cancers, clinical data are lacking. In contrast, the rather limited epidemiologic data suggest that soy could increase risk of BC; however, the animal studies show just the opposite.

Epidemiologic evidence suggesting that soy decreases risk of LC among non-smokers is particularly intriguing because expression of the oncogene that is increased in tumors from non-smokers may be suppressed by genistein. The skin cancer data are much too limited to meaningfully speculate about a role for soy, whereas the thyroid cancer data provide considerable assurance that soy does not increase risk of this cancer.

Finally, it is important to emphasize that most of the epidemiologic data relevant to understanding the impact of soy intake on cancer risk comes from studies involving Asian populations. These studies are valuable because, unlike the situation in non-Asian countries, soy consumption is less likely to identify individuals that differ markedly from their non-soy consuming counterparts, so confounding is less of an issue. On the other hand, there are always concerns about extrapolating the results from one ethnic group to another. Since in general soy intake is low among non-Asian populations, meaningful insight into the soy/cancer relationship is most likely to come from Western cohort studies such as the Adventist Health Study-2 and the Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC), which include significant numbers of high-soy-consumers.

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Continued on pg. 6

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CANCER TRENDS WORLDWIDE AND ACROSS AMERICA

By Christine Werner, PhD, PA-C, RD

One out of every third individual will encounter a cancer diagnosis in his or her lifetime.[1] While projections indicate approximately 22 million Americans will be diagnosed with cancer over the next 20 years, more people are surviving their cancers and death rates from cancer are declining,[1] in part due to improved screening, detection and treatment advancements. This article describes distinct patterns and trends of cancer rates and deaths worldwide and in the United States, according to most recent published data.

Cancer Worldwide

Cancer is the second most common cause of death worldwide; cardiovascular disease ranks first.[2] Developed countries have higher cancer incidence and mortality rates than less developed or developing countries, regardless of gender.

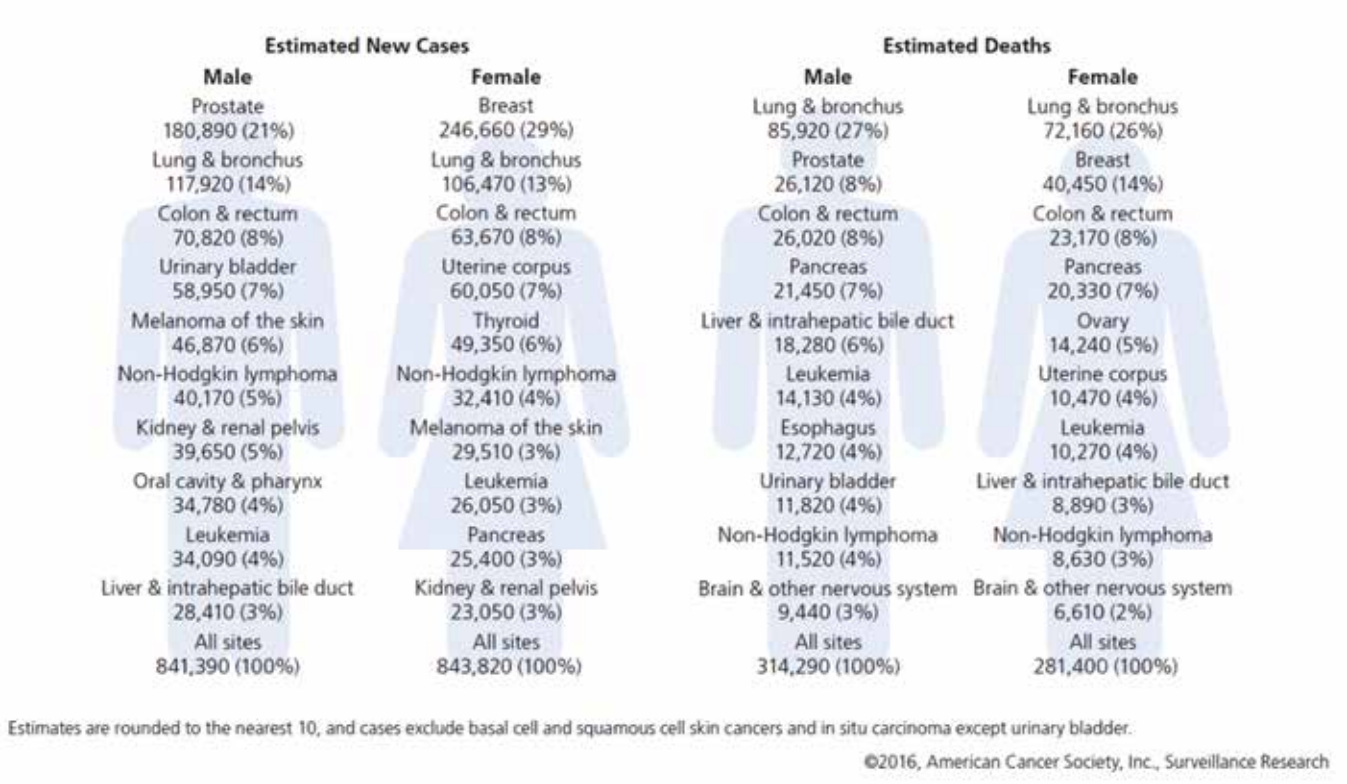
Cancers of the lung, prostate, colon and rectum (colorectal) are the most commonly diagnosed cancers in men while cancers of the breast, colorectal and lung are the top three diagnosed cancers in women.[2] Lung cancer continues to be the leading cause of cancer death in men followed by prostate cancer, while breast cancer is the leading cause of cancer-related death in women, followed by lung cancer.[2,3] Cancers due to infectious etiology are more prevalent in developing countries, with stomach cancer the most reported, followed by liver and cervix cancers.

Cancer Trends Among U.S. Men

Prostate and skin cancer are the most commonly diagnosed cancers among American men, followed by cancer of the lung and bronchus and colon and rectum.[3,4] Rates of prostate cancer have decreased over the past ten years, though it is still the second highest leading cause of cancer death (8%), followed closely by colon and rectum (8–9%). The rate of death from prostate cancer is higher among African Americans than men of any other racial or ethnic groups.[2,5]

Mortality from lung and bronchial cancer continues to be *the most common* type of fatal cancer among men even though incidence trends have decreased the past 10–15 years.[1-3] Many trends in cancer incidence and mortality rates reflect advancement in diagnostic screenings (i.e., PSA blood test, mammography, colonoscopy, Pap/HBV test, etc.), public health/risk factor education (cigarette smoking, genetic/familial inheritance) and expansion of medical treatment modalities.

Leading Sites of New Cancer Cases and Deaths—2016 Estimates



Estimated New Cases		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 180,890 (21%)	Breast 246,660 (29%)	Lung & bronchus 85,920 (27%)	Lung & bronchus 72,160 (26%)
Lung & bronchus 117,920 (14%)	Lung & bronchus 106,470 (13%)	Prostate 26,120 (8%)	Breast 40,450 (14%)
Colon & rectum 70,820 (8%)	Colon & rectum 63,670 (8%)	Colon & rectum 26,020 (8%)	Colon & rectum 23,170 (8%)
Urinary bladder 58,950 (7%)	Uterine corpus 60,050 (7%)	Pancreas 21,450 (7%)	Pancreas 20,330 (7%)
Melanoma of the skin 46,870 (6%)	Thyroid 49,350 (6%)	Liver & intrahepatic bile duct 18,280 (6%)	Ovary 14,240 (5%)
Non-Hodgkin lymphoma 40,170 (5%)	Non-Hodgkin lymphoma 32,410 (4%)	Leukemia 14,130 (4%)	Uterine corpus 10,470 (4%)
Kidney & renal pelvis 39,650 (5%)	Melanoma of the skin 29,510 (3%)	Esophagus 12,720 (4%)	Leukemia 10,270 (4%)
Oral cavity & pharynx 34,780 (4%)	Leukemia 26,050 (3%)	Urinary bladder 11,820 (4%)	Liver & intrahepatic bile duct 8,890 (3%)
Leukemia 34,090 (4%)	Pancreas 25,400 (3%)	Non-Hodgkin lymphoma 11,520 (4%)	Non-Hodgkin lymphoma 8,630 (3%)
Liver & intrahepatic bile duct 28,410 (3%)	Kidney & renal pelvis 23,050 (3%)	Brain & other nervous system 9,440 (3%)	Brain & other nervous system 6,610 (2%)
All sites 841,390 (100%)	All sites 843,820 (100%)	All sites 314,290 (100%)	All sites 281,400 (100%)

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Additional types of cancers have been reported more prevalent in men than women according to recent estimates.[3,4] The incidence of kidney/bladder, oral cavity and pharynx cancers is more than twice as high among men, while that of liver cancer is three times higher among men than women.[3,4]

Leukemia and lymphoma are two cancers that continue to be among the top ten cancers affecting both men and women. The incidence of leukemia and lymphoma have increased over the past few decades while deaths rates for both have decreased over time.[2,4]

While melanoma makes up only 1% of all skin cancer diagnoses, it accounts for the majority of all skin cancer deaths.[3,6] In 2016, it was projected there would be over 76,000 new diagnoses of melanoma, and greater than 10,000 patient deaths from this type of skin cancer.[3] Incidence rates of melanoma increase in men over 50, while rates of melanoma are higher in women before the age of 50.[3,6]

Cancer Trends Among U.S. Women

Breast cancer is the most commonly diagnosed cancer among American women and is the second leading cause of cancer death.[2,3] Lung cancer is the leading cause of cancer death in women, while colon and rectal (colorectal) cancer is third.[1-3] Death rates from breast cancer have fallen over the past 20 years in part due to earlier detection and improvements in treatment.

The incidence of ovarian cancer has steadily declined over the past ten years though it is still the leading cause of death among the reproductive organ cancers. In comparison, the incidence of endometrial cancer has been mildly rising (1.3–1.9% annually), regardless of the age of the women.[3] Cancers of the anus, gallbladder and thyroid all have higher incident rates among women than men although the rate of thyroid cancer is three times higher than the others. The death rate from thyroid cancer is equal to that of men.[4]

Conclusions

Cancer is a significant global health concern. One in every seven deaths worldwide are caused by cancer.[1-3] Risk of developing cancer increases with age. It is predicted that in the U.S., 21.7 million new cancer diagnoses will be made, and that 13 million cancer deaths will occur by 2030.[2-3] Unhealthy eating patterns, physical inactivity, genetics, and many other environmental factors play important roles in the etiology of several cancers.[1-3]

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SOYBEAN OIL CORNER

OBSERVATIONAL STUDIES SHOW OMEGA-6 PUFA LOWERS CVD RISK, IS NOT PROINFLAMMATORY

By Mark Messina, PhD, MS

Newly published epidemiologic research goes a long way toward addressing two highly debated issues related to the health implications of dietary fat. More specifically, Chinese researchers provide evidence which supports a considerable amount of clinical data showing that the consumption of omega-6 polyunsaturated fat (PUFA) is not proinflammatory. In addition, U.S. researchers show that dairy fat can increase risk of cardiovascular disease, but whether it does depends upon the macronutrient that replaces it in the diet.

The Chinese research consisted of a cross-sectional study involving 269 healthy participants (25–80 years old) from the Singapore Prospective Study Program who were selected by virtue of their falling into one of three predetermined dietary groups based on their fish and meat intake.[1] Collectively, the results showed that high intake of red meat and high intake of fish increased plasma levels of arachidonic acid (AA). In contrast, neither the intake of omega-6 PUFA nor the intake of omega-6-PUFA-rich cooking oils (including soybean oil) was related to AA levels. However, such intakes were associated with higher levels of alpha-linolenic acid (ALA). Since fish and red meat are high in AA, these data show that preformed AA, but not its precursor linoleic acid, is an important determinant of AA status. Consequently, these data refute concerns that omega-6 PUFA are proinflammatory. These concerns are based on the assumption that the intake of omega-6 PUFA increases endogenous levels of AA, which in turn will lead to the synthesis of proinflammatory eicosanoids.

The U.S. research consists of an analysis of data from three cohort studies: the Health Professionals Follow-Up Study (n=43,652 men), the Nurses' Health Study (n=87,907 women), and the Nurses' Health Study II (n=90,675 women).[2] Dairy fat and other fat intakes were assessed every four years using validated food-frequency questionnaires. During 5,158,337 person-years of follow-up, there were 14,815 incident cardiovascular disease cases including 8974 coronary heart disease cases (nonfatal myocardial infarction or fatal coronary disease) and 5841 stroke cases.

Compared with an equivalent amount of energy from carbohydrates (excluding fruit and vegetables), dairy fat intake was not significantly related to risk of total CVD, coronary heart disease or stroke. However, replacement of 5% of energy intake from dairy fat with equivalent energy intake from PUFA was associated with a statistically significant 24% lower risk of CVD, whereas the 5% energy intake substitution of other animal fat with dairy fat was associated with a statistically significant 6% increased CVD risk. These data emphasize the important role that PUFA has in lowering risk of CVD.

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