



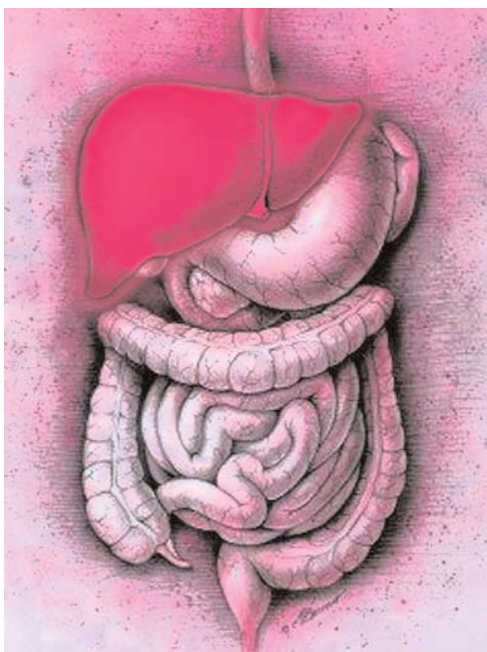
A new trial in high-risk patients shows ...

Menatetrenone

Gives Hope Against HCC Liver Cancer!

Hepatocellular carcinoma (HCC, also known as primary liver cancer or *hepatoma*) is the most common primary, malignant liver tumor, and the fifth most common cancer in the world, with about 430 000 people suffering from it worldwide in 1990. It's as deadly as it is common: almost everyone who develops HCC will die within a year.

The single largest risk factor for HCC is viral hepatitis. In fact, if you have chronic **hepatitis B** infection, your risk of HCC *climbs two hundred fold* over the rest of the population. (Other risk factors include **Hep C**, **aflatoxin** (a toxin produced by some molds in food), some **drugs** and **industrial chemicals** (such as vinyl chloride), **alcohol abuse**, **non-viral hepatitis**, and the iron-metabolism disorder **hemochromatosis**).



With the prognosis for HCC so hopeless, any way to reduce the risk of developing HCC in high-risk patients would be considered a **Godsend**. So based on a paper just published in the prestigious *Journal of the American Medical Association (JAMA)*, many people may start thinking of Menatetrenone as

a little bit of divine intervention.¹

Menatetrenone is one of the three major forms of "vitamin K" in the diet. *Phylloquinone* (vitamin K₁) is produced by plants, and is primarily used in humans and other mammals in the liver to support blood clotting. A wide range of

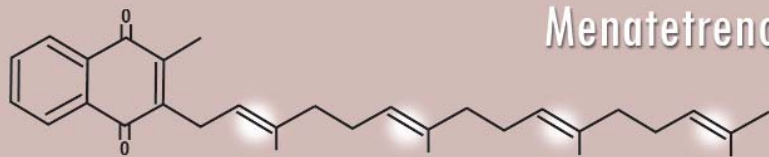
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"menaquinones" are produced by different organisms; collectively, these are termed "Vitamin K₂." Bacteria primarily produce a menaquinone called MK-7. Most supplements labeled "vitamin K₂" or "menaquinone" contain MK-7. **Menatetrenone**, or MK-4, is the menaquinone biosynthesized by mammals which is concentrated in the brain and vasculature and plays an important role in their health. **Multiple clinical trials have documented the power of Menatetrenone to protect bone health**, reducing the risk of fracture in women with postmenopausal osteoporosis and other threats to bone health.^{2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23}

A group of Japanese researchers were performing a clinical trial to test the effects of MK-4 against bone loss in women with **viral liver cirrhosis**, who are vulnerable to osteoporosis because they malabsorb calcium, vitamin D, and other key nutrients. Indeed, over the course of the two-year trial, they found that women taking **Menatetrenone** were protected against *more than half* of the loss of bone mineral density suffered by women taking the sugar pills.⁸ However, the researchers wondered if **Menatetrenone** might *also* protect these high-risk women against their increased hazard of HCC.

This wasn't an idle speculation. There have long been hints that **Menatetrenone** might have power against cancer - including HCC. In test-tube studies involving a wide range of cancer cell types, **Menatetrenone has been shown to slow the growth, induce apoptosis (cellular "suicide"), and reduce the aggressiveness of a wide range of cancer cell types.**^{24,25,26,27,28,29,30,31,32,33,34,35} When studies have compared the effects of **Menatetrenone** to its cousin Ks, they have found some intriguing differences in mechanism of action and ultimate effect which make the powers of **Menatetrenone** all the more remarkable. In cell culture studies, researchers have found that menadione ("vitamin K₃" - a purely artificial molecule formed by stripping the molecular "tail" from phylloquinone (regular vitamin K₁), and which is toxic at higher doses) kills healthy cells and cancer cells *alike*,^{28,30} whereas **Menatetrenone selectively kills tumor cells**, leaving healthy ones intact.²⁸

This discrepancy is the result of the two vitamers' different effects at the molecular level: whereas menadione kills healthy and cancer cells alike by indiscriminately flooding



Menatetrenone

them with free radicals,^{28,30} **Menatetrenone** turns on a cell suicide program at the gene expression level, apparently acting through its side chain.³⁰ Phylloquinone has some effects against cancer cells in some models, but its effects are much less potent than those of **Menatetrenone**: in oral tumor cell lines and leukemia cells, for instance, **Menatetrenone** is ten times more effective than K₁,²⁸ whereas in brain cancer cells **Menatetrenone** inhibits cell growth while phylloquinone is totally ineffective.³⁰ Some of the most remarkable effects have been observed in **leukemia** cells, in which it has been found that **in those cancer cells that Menatetrenone doesn't kill outright, it often actually induces differentiation** - the "taming" of cancer cells back into their normal, healthy structure and function.^{27,29,35}

However, as watchers of overhyped supplements will know, lots of things will kill cancer cells - in a test tube. While these "in vitro" studies can tell us a lot about why certain things happen in the body, they don't, in themselves, prove that anything will happen. To do that, you need studies in living, breathing organisms - preferably, human beings, in controlled clinical trials.

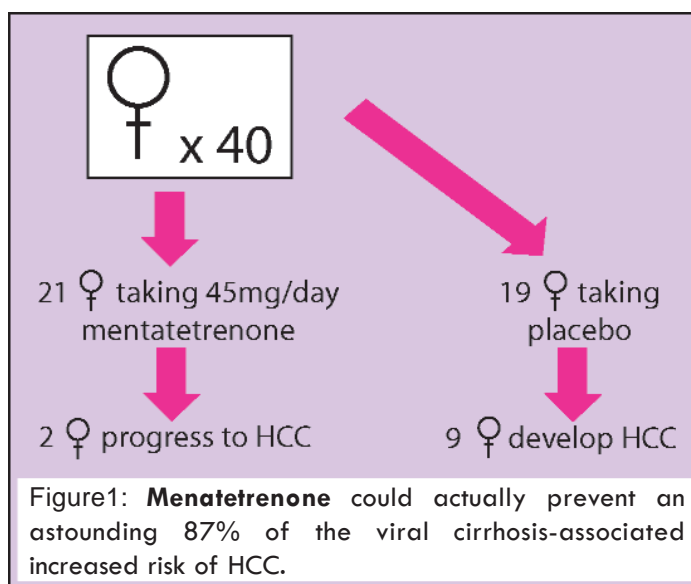
Research had already begun to provide some evidence that the effects of **Menatetrenone** aren't confined to glassware. Case studies and small clinical trials have reported that **Menatetrenone can help to normalize blood cell production in myelodysplastic syndrome (MDS)**,^{36,37,38,39,40} a rare disorder caused by damage to blood stem cells in the bone marrow, leading to low levels of many blood cell types and (too often) to leukemia. In one remarkable case study, published in the *British Journal of Haematology*,⁴¹ Menatetrenone - combined with all-trans retinoic acid, enocitabine, and daunorubicin - induced complete remission of relapsing acute promyelocytic leukaemia in a 72-year-old woman! This single promising case is certainly not proof until a proper clinical trial has been performed, but it opened up the exciting possibility that **Menatetrenone** supplementation might improve the effects of conventional chemotherapy.

HCC looked like an especially promising target for a clinical trial. Abnormal vitamin K metabolism is a feature of HCC, and the extent of these abnormalities correlates strongly with their risk of developing **portal venous invasion**, the most common way that a "benign" liver tumor executes its lethal spread.^{42,43,44,45,46} Cell culture studies confirm that **Menatetrenone** inhibits the growth of HCC

cells and their tendency to invade healthy tissue.²⁴ While the study is not yet complete, scientists have already reported the preliminary results of a trial which appears to be showing that over the course of two years, **Menatetrenone supplementation cut the risk of HCC victims going on to suffer a deadly portal venous invasion by more than 75%**, from 55% in the control group down to just 13% in the **Menatetrenone** supplementers!⁴⁷

With all of this promising information as background, the researchers who had run the controlled trial that showed that MK-4 is effective against *bone loss* in women with viral cirrhosis decided to find out if it might protect them from developing HCC. In a randomized, double-blind, placebo-controlled trial, forty women with the disease had been randomly assigned to take either a **Menatetrenone** supplement (45 milligrams a day) or a dummy pill for two years.¹

At the end of the trial, nine of the 19 women taking the placebo were struck by HCC - compared to just 2 of the 21 women who had taken MK-4. In other words, **people taking Menatetrenone were five times less likely to develop**



hepatocellular carcinoma than women taking the dummy pills!¹

In fact, this result appears to have *underestimated* the power of **Menatetrenone** to prevent viral cirrhosis from going on to cause HCC. When the researchers compared the two groups' blood tests and medical history, they found that the women who had taken MK-4 supplements were actually at *higher* risk of developing HCC than the women in the control group. After adjusting for these factors using statistical models, the researchers concluded that **Menatetrenone** could actually prevent an astounding 87% of the viral cirrhosis-associated increased risk of HCC.

The scientists were cautious about the results of their trial, noting the small size of their study, the early development of HCC in some members of the control group, and the tumor grades observed. "Nonetheless," they concluded, "our study indicates that [Menatetrenone] decreases the risk of hepatocellular carcinoma ... The results of this preliminary trial are intriguing and suggest that a potential role for [Menatetrenone] to prevent hepatocarcinogenesis in patients with liver cirrhosis [exists]. These results must be confirmed by multicenter randomized controlled studies".

To which we can only say: hear, hear!

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