

3.2.1.2 *Can Modulating the Insulin–IGF1 Pathway Increase Lifespan in Human Beings?*

Another way to determine whether modulation of metabolism could increase lifespan would be to test whether the insulin–IGF1 pathway regulating metabolism and responses to a food shortage in very different species (*e.g.* nematodes, flies, rodents, humans) can modulate lifespan. Dwarf mice bearing mutations of this pathway live longer,¹⁹ but no such increase has been observed in dwarf human mutants.²⁰ In addition, the effect on lifespan of genetic polymorphisms at loci governing metabolism has been tested in human beings and it has been reported that FOXO3A gene polymorphisms were linked to longevity. These studies compared very long-lived subjects (>90 years) to younger controls and a meta-analysis concluded that some variants were linked to very high longevity, at least in one sex.²¹ However, these studies compare living persons, a first cohort being composed of very old subjects and the second control cohort comprising younger subjects, and there is no grounds to argue that persons of the second cohort will live less than those of the first one. In other words, the real longevity difference between the two cohorts, when they will be extinct, could be low or even absent. This conclusion is strengthened by the fact that a significant effect reported in a study comparing the oldest-old Danes to a 30–50 years younger cohort was not observed when linking the longevity of individuals of the oldest cohort (all persons were dead at this time but one) with the very same polymorphism (variant rs7762395).²² In addition, a later study reported small differences in the prevalence of this rs7762395 variant between different birth cohorts observed at the same ages (>95 years, cohorts born from 1895 to 1915), which shows that factors other than longevity could explain polymorphism.²³ Could it be that differences between birth cohorts separated by several decades could give rise to differences not linked to age?

A direct test of a link between IGF-1 and remaining lifespan was tested in nonagenarians.²⁴ The plasmatic IGF-1 level was not linked to lifespan in men, but women with a level below the median survived longer. However, in the subgroup with a history of cancer (23% of the cohort: 34/151) subjects with a high IGF-1 level died before those with a low one, no such effect being observed in people without cancer (77% of the cohort). Because the whole cohort comprised *ca.* 75% women, it seems clear that the effect observed in people with cancer is mainly due to women. Thus, it can be said that in nonagenarian women with a history a cancer, those with a high IGF-1 level survived less than those with a low level, but such an effect is not observed in women without cancer and in all men. Because IGF-1 promotes metabolism, it is not surprising that people with a high IGF-1 level have a higher cancer risk (*i.e.* a higher risk for an anarchic cellular proliferation), but the main result of this study is the absence of a link between IGF-1 level and remaining lifespan in people without cancer. Obviously, it would be of interest to replicate this study with younger people.