Module 2.4.

Antioxidants

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Learning objectives:

- To understand what oxidative stress and antioxidants are;
- To be able to list antioxidants by category;
- To learn about the methods used to assess antioxidant status;
- To understand the mechanisms underlying the antioxidant effects of specific vitamins and trace elements;
- To understand the role of antioxidant vitamins and trace elements in health;
- To know about the effects of antioxidant vitamins and trace elements in disease states.

Contents:

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Key Messages:

- To minimize the effects of oxidative stress on the body, it is important to ensure appropriate intake of dietary antioxidants;
- Dietary antioxidants are found particularly in the form of vitamins A, C, and E, and as the trace element selenium;
- Oxidative stress can lead to a variety of diseases including cancer, cardiovascular disease, non-alcoholic fatty liver disease, dementia, and macular degeneration;
- Antioxidant supplementation may decrease risk and improve disease outcomes, especially in critically ill patients;
- Although consumption of dietary antioxidants can be beneficial, pharmacological doses of supplemental antioxidants in the healthy can occasionally have deleterious effects.

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1. Vitamin and Trace Element Antioxidants: Functions, Mechanisms, and Methods of Assessment

1.1. Introduction to Oxidative Stress and Antioxidants

Oxidative stress occurs when there is an imbalance due to a greater amount of oxidants than antioxidants. Oxidants are produced in the body during normal metabolism and are most often found in the form of reactive oxygen species (ROS) or free radicals. Free radicals pose a danger because they have an unpaired electron that is free to react with other compounds, thus oxidizing them. Oxidation of lipids, DNA, and proteins can be especially damaging to the body and cause chronic disease. To prevent oxidative damage, it is essential to have enough antioxidants. Antioxidants react with these damaging compounds, reducing them, and thereby neutralizing them (**see Fig. 1).**

In the food industry, the study of antioxidants is mainly focused on the prevention of rancidity which occurs due to lipid peroxidation. In the realm of healthcare, the study of antioxidants is centred on disease treatment and prevention.

Several different categories of antioxidants exist. Antioxidant vitamins A, C, and E are found in a variety of plant sources. Selenium is a mineral that is essential in the function of the antioxidant enzyme glutathione peroxidase. Other dietary antioxidants include zinc, polyphenols and flavonoids. Within the body, there are also endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. For the purpose of this module, our focus will be on the antioxidant vitamins and the antioxidant trace element selenium.

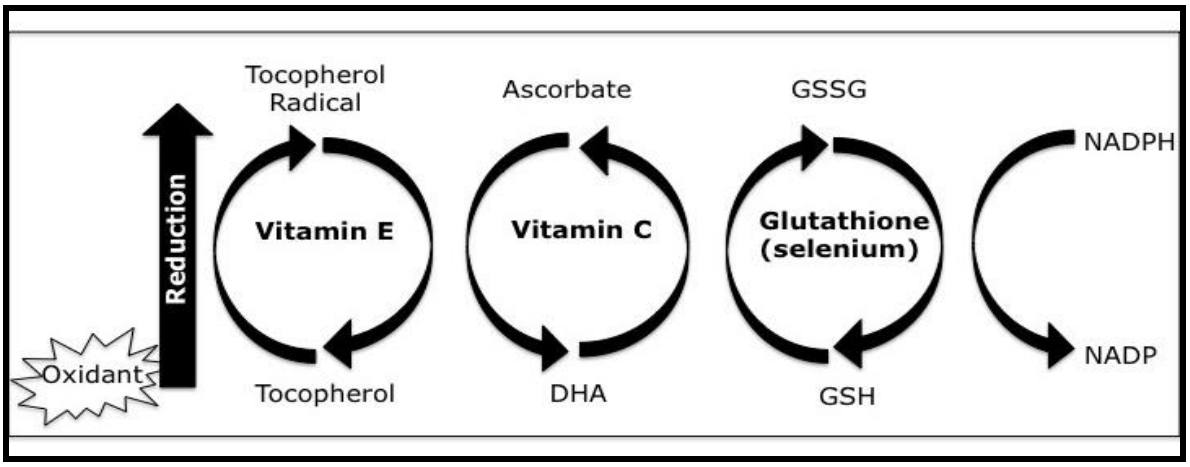

Fig. 1. Synergistic action of common antioxidants. Pro-oxidant compounds can be reduced to their safe form by several different mechanisms including reduction of tocopherol (vitamin E), reduction of ascorbate (vitamin C) to DHA, or reduction of glutathione. The antioxidant can then be regenerated following reaction with a reducing agent such as NADPH

*DHA: Dehydroascorbic acid, GSSG: Glutathione Disulfide, GSH: Glutathione NAPD: Nicotinamide Adenine Dinucleotide Phosphate

1.2. Methods of Assessment

There are two main methods for assessing oxidant status: measurement of markers of oxidation (oxidative stress), and measurement of specific antioxidant levels.

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There are several laboratory methods to assess oxidative stress. Examples include the erythrocyte haemolysis test which measures the ability of the red blood cell to resist oxidative damage. Breath pentane and ethane can also be used to measure oxidative stress. Pentane and ethane are the lipid peroxidation products of linolenic and linoleic acids respectively (1). There is a vast number of other specific biomarkers for oxidative stress status, however there is no consensus on which are the best markers for clinical use (2).
Markers of specific antioxidant levels include total serum vitamin A, serum carotenoids, serum α-tocopherol, serum ascorbic acid, and plasma selenium. It is important to remember that serum/plasma levels of these antioxidant can often be affected by a wide range of factors including age, race, smoking status, pregnancy, and infection. Alternatively, dietary intake (including supplements) can be used to estimate the antioxidant status.

1.3. Antioxidant Vitamins

Humans obtain antioxidants from naturally-occurring plant sources of antioxidant vitamins. Plants naturally produce antioxidants as a defence to ROS produced during the process of photosynthesis. These antioxidants are consumed by humans when we eat the plants in the form of vitamin A, carotenoids, and vitamins C, and E**.** **Table 1** shows the antioxidant power of several commonly consumed fruits and vegetables. This section will focus on the role of each of these vitamins in mediating the effects of oxidative stress.

Table 1: Total radical-trapping antioxidant potential of commonly consumed fruits and vegetables. Expressed as µM Trolox equivalent (µMTE) per 100g. Adapted from Serfini *et al.,* 2002 (7).

Antioxidant Potential	**Food sources**
High (>1000µMTE/100g)	Garlic, kale, spinach
Medium (500-1000µMTE/100g)	Broccoli, orange
Low (<500µMTE/100g)	Onion, potato, cabbage, carrots, tomato, apple, pear

1.3.1. Vitamin A and Carotenoids

Vitamin A is a family of fat-soluble compounds including retinol, retinal, and retinoic acid that are important for vision, immune function, and growth and development(3). Dietary vitamin A falls into one of two categories, pre-formed vitamin A and the pro-vitamin A carotenoids beta-carotene, alpha-carotene, and beta-cryptoxanthin which can be converted into retinal in the body (3).
Carotenoids can directly scavenge free radicals and quench singlet oxygen species. However, carotenoids can also act as pro-oxidants under certain conditions such as at high O_2 concentrations (4).
Studies have found that supplementation with beta-carotene (but not vitamin A) actually causes an increase in lung cancer risk in smokers and asbestos workers. This is because at high partial pressures of O_2, such as those in the lungs, beta-carotene may act as a pro-oxidant instead of an antioxidant. Thus, beta-carotene is not a recommended supplement for those already at high risk for lung cancer (4,5).

1.3.2. Vitamin C

Vitamin C (or ascorbic acid) is a water-soluble vitamin which functions as a cofactor in many reactions due to its function as a reducing agent. This property of vitamin C makes it an important antioxidant in the body. Vitamin C is especially important as it also functions to regenerate other antioxidants including alpha-tocopherol (vitamin E) and glutathione

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peroxidase. Since vitamin C is water-soluble, it is a significant antioxidant in the plasma, where it acts to quench aqueous peroxyl radicals (4). Oxidation of vitamin C that occurs in quenching reactions results in formation of dehydroascorbic acid (DHA) (**see Fig. 2**). DHA can be reduced back to vitamin C by reaction with glutathione (4).
Vitamin C requirements are higher for smokers due to the increase in oxidative damage faced by the lungs of smokers. Vitamin C is present in the extracellular fluid lining of the lungs where it can quench any radicals produced by smoking (6). Increased requirements are also necessary for severely ill patients due to increased tissue uptake of vitamin C.

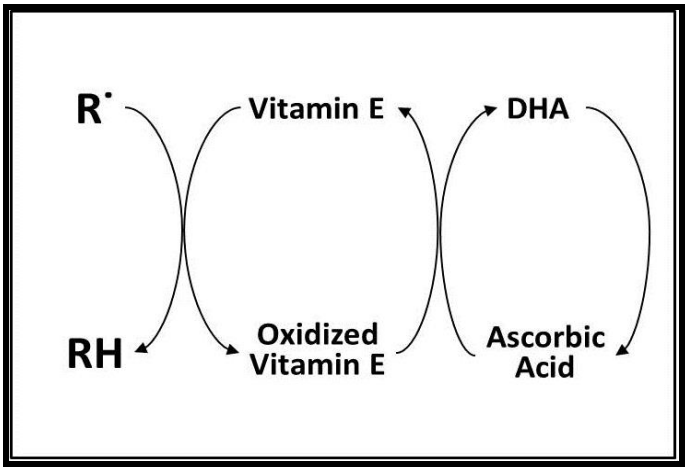

Fig. 2. Oxidation of vitamin C to DHA regenerates oxidized vitamin E. Free radicals ($R^{\bullet}$) such as the hydroxyl radical ($HO^{\bullet}$) are reduced to a stable form (H_2O) by vitamin E. Vitamin E is then regenerated by ascorbic acid.
* DHA: Dehydroascorbic acid, R represents a free radical molecule (RH is the reduced form)

1.3.3. Vitamin E

Vitamin E is actually a class of 8 lipid-soluble compounds known as tocopherols and tocotrienols. These are in the form of α-, β-, γ-, and δ-tocopherols and tocotrienols, with α-tocopherol being the most biologically active form in humans. The main antioxidant function of vitamin E is in the prevention of lipid peroxidation by protection of the phospholipid bilayer of the cell membrane. It is also an important line of defence for preventing the oxidation of LDL which is a key step in the development of atherosclerosis (4).

1.4. Antioxidant Trace Elements (Selenium)

Selenium and zinc are both trace elements that have a function in antioxidant defence. Our focus will be on selenium due to its important role in the enzyme glutathione peroxidase (GPx). Selenium in itself is not an antioxidant but it is required for the function of the antioxidant enzyme GPx. Within enzymes, the selenocysteine residue in selenoproteins catalyzes the reduction of pro-oxidants (4). GPx acts to reduce hydrogen peroxide to water and lipid hydroperoxides to their corresponding alcohols (**see Fig. 3**).

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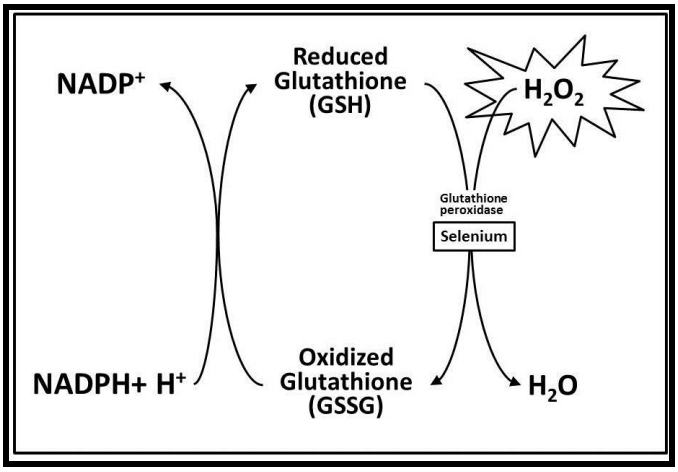

Fig. 3. Mechanism of glutathione peroxidase in reduction hydrogen peroxide. The reactive oxygen specie H_2O_2 is reduced to H_2O by glutathione peroxidase which contains selenium in its active site. NADPH (Nicotinamide Adenine Dinucleotide Phosphate) is a reducing agent required for the regeneration of GSH.

Several studies have assessed the effect of selenium supplementation. One of these, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a large prospective study of 35,533 men without prostate cancer where participants were randomized into four groups: vitamin E and selenium supplements, vitamin E supplement and placebo, selenium supplement and placebo, and both placebos and monitored every six months. Results showed that men in the vitamin E supplement group had a significantly higher risk of developing prostate cancer. This effect was not seen in the vitamin E + selenium supplement group, suggesting a possible protective effect for selenium (7). This is an example of how supplemental antioxidants at high doses can have deleterious effects in healthy individuals as the dose of synthetic vitamin E administered was 12x higher than the recommended daily allowance of vitamin E. Several meta-analyses have shown no relationship between vitamin E supplementation and prostate cancer risk (**see Table 2**) so it is possible that there is a dose-response relationship in which very low and very high intakes of vitamin E are associated with adverse effects.

2. Antioxidants in disease states

Oxidative damage can lead to a host of different diseases including cancer, cardiovascular disease, lung disease, and many others. Many studies have been conducted to evaluate the efficacy of antioxidants on treatment and prevention of various diseases. Results are varied and show that antioxidants are no panacea; however they generally don't cause harmful effects and may occasionally be beneficial.

2.1. Cancer

Cancer is one of the leading causes of death worldwide. Oxidative damage to DNA results in DNA mutations, characteristic of tumours. For this reason, antioxidant therapies may be more effective for prevention rather than treatment of various cancers. It is also important to note that many cancer treatment strategies (chemotherapy, radiation, surgery, etc.) cause oxidative stress. **Table 2** lists the results of various meta-analyses on the effect of antioxidants on cancer, listed by cancer type.

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Table 2: Effects of antioxidants on cancer, by cancer type

Reference	Study population	Antioxidants/Diseases Studied	Results
Colorectal Cancer			
Arain & Abdul, 2010 (8)	4 RCTs (94,064 participants)	Vitamin E and prevention of colorectal cancer	- All four trials reported non-significant effects of vitamin E supplementation on colorectal cancer
Ou *et al*., 2012 (9)	7 studies: 2136 cases, 2065 controls	Selenium status and colorectal adenoma risk	-Pooled OR for colorectal adenoma risk for highest vs. lowest Se level was 0.67 (95% CI: 0.55-0.81)
Papaioannou *et al*., 2011 (10)	12 studies (n= 148,922)	Antioxidants and prevention of colorectal cancer and colorectal adenomas	- RR of developing colorectal cancer in populations taking antioxidant supplements vs. no supplements = 1.00 (95%CI: 0.88-1.13) -RR for developing an adenoma = 1.47 (95%CI: 0.97-2.23)
Takata *et al*. 2011 (11)	15 studies (WHI, 12 observational studies, 2 clinical trials)	Comparing results of the Women's Health Initiative study on selenium and colorectal cancer with previous studies	- High [Se] were not associated with increased colorectal cancer risk (p=0.10) in WHI study - From the meta-analysis, no significant association between selenium status and colorectal cancer risk in women, however in men there was a significant inverse relationship (p=0.01)
Lee *et al*. 2011 (12)	2 RCTs	Selenium and cancer risk (main outcome = cancer incidence).	- RR 0.72 (95%CI: 0.30-1.72)
Myung *et al*., 2010 (13)	7 RCTs	Antioxidant supplements on cancer incidence. Main outcome: cancer incidence.	- RR 0.97 (95%CI: 0.84-1.12)
Bjelakovic *et al*., 2008 (14)	20 randomised trials (211,818 participants)	Beta-carotene, vitamins ACE, and selenium on colorectal cancer prevention.	-Antioxidant supplements had no overall effect on colorectal cancer risk (RR 0.97, 95%CI: 0.86-1.09) -For antioxidants alone or in various combination, results were still not significant
Park *et al*., 2010 (15)	13 cohort studies (676,141 subjects)	Colon cancer and vitamins ACE.	- Comparing highest vs. lowest quintiles of total intake, the pooled, multivariate RR was 0.81 (95% CI: 0.71–0.94) for vitamin A, 0.84 (95% CI: 0.74–0.95) for vitamin C, and 0.83 (95% CI: 0.73–0.94) for total vitamin E -After adjusting for folate intake, the results for vitamin A were no longer significant
Jeon *et al*., 2011 (16)	3 RCTs	Beta-carotene on cancer prevention. Primary outcome: total cancer incidence and mortality	- RR 0.98 (95%CI: 0.81-1.19)

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Dennert *et al*., 2011 (17)	5 studies	Selenium and cancer. Primary outcome measures: incidence of any cancer and cancer-related mortality	-OR 0.89 (95%CI: 0.65-1.23) -After gender stratification- still non-significant
Prostate Cancer			
Jiang *et al*., 2010 (18)	9 RCTs	Antioxidant vitamins and selenium on prostate cancer risk and mortality.	-No significant difference in prostate cancer incidence or mortality in patients supplemented with beta-carotene, vitamin C, vitamin E, or selenium
Stratton & Godwin, 2011 (19)	14 studies	Vitamin and mineral supplements and prostate cancer. Primary outcomes: occurrence of prostate cancer, advanced/metastatic prostate cancer or death due to prostate cancer.	-Overall, there was found to be no significant evidence supporting the use of vitamin/mineral supplements in the prevention or treatment of prostate cancer
Dennert *et al*., 2011 (17)	14 studies	Selenium and incidence of prostate cancer.	-OR 0.78 (95%CI: 0.66-0.92)
Lee *et al.,* 2011 (12)	2 RCTs	Selenium and prostate cancer risk (main outcome = cancer incidence).	-RR 0.67 (95%CI: 0.25-1.74)
Myung *et al.,* 2010 (13)	7 RCTs	Antioxidant supplements on prostate cancer incidence.	- RR 0.84 (95%CI: 0.69-1.02)
Jeon, *et a.,* 2011 (16)	2 RCTs	Beta-carotene on prostate cancer prevention. Primary outcome: total cancer incidence	- RR 1.02 (95%CI: 0.93-1.12)
Lung Cancer			
Cortés-Jofré *et al*., 2012 (20)	9 studies	Antioxidants (vitamins ACE, selenium) and lung cancer. Primary outcomes: lung cancer incidence and lung cancer mortality *Note vitamin A in this study does not include beta-carotene	-No significant amelioration for vitamins A, C, E, and selenium when taken alone or in various combinations -For a combination of A,C,E, and selenium vs. placebo: RR for all-cancer mortality in women was 0.79 (95%CI 0.64-0.98) and RR for all-cause mortality was 0.95 (95% CI 0.91 to 0.99)
Fritz, 2011 (21)	130 studies	Selenium and lung cancer	-37/41 preclinical studies showed support for anti-cancer effect of selenium -Evidence suggests that moderate, but not very high doses of selenium confer the most protection against lung cancer -The greatest effect was seen in populations with already low selenium status
Fritz *et al*., 2011 (3)	248 studies	Vitamin A and lung cancer. Included trials assessing the efficacy of natural or synthetic retinoids in lung cancers for the purposes of	-54/67 pre-clinical studies found significant results supporting vitamin A for the prevention of lung cancer -Insufficient evidence to support the use of vitamin A and retinoids for

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		treatment, prevention, and reduction of side effects associated with chemo- or radiation- therapy	the treatment/prevention of lung cancer
Lee *et al.,* 2011. (12)	3 RCTs	Selenium and lung cancer risk (main outcome = cancer incidence).	- RR 0.83 (95%CI: 0.51-1.35)
Myung *et al.,* 2010 (13)	7 RCTs	Antioxidant supplements on lung cancer incidence.	- RR 1.00 (95%CI: 0.83-1.20)
Jeon *et al.,* 2011 (16)	4 RCTs	Beta-carotene on cancer prevention. Primary outcome: total cancer incidence	- RR 1.08 (95%CI: 0.93-1.25)
Dennert *et al.,* 2011 (17)	11 studies	Selenium and cancer. Primary outcome measures: incidence of any cancer and cancer-related mortality	-Risk estimate of 0.75 (95%CI: 0.54-1.03) -After gender stratification: non-significant
Druesne-Pecollo *et al.,* 2010 (5)	8 RCTs (180,702 subjects)	Beta-carotene on lung cancer incidence	- RR 1.20 (95%CI: 1.07-1.34) in smokers and asbestos workers - Overall RR 1.01 (95%CI: 0.98-1.04)
GI Cancer			
Bjelakovic *et al.,* 2008 (14)	20 randomised trials (211,818 participants)	Beta-carotene, vitamins ACE, and selenium on GI cancer prevention. Outcome measures: GI cancer, overall mortality, and adverse effects.	-Antioxidant supplements had no overall effect on GI cancer risk (RR 0.94, 95%CI: 0.83-1.06) -Meta-regression analysis showed that dose of selenium was associated with a significantly lower risk of GI cancer (RR 0.996,95% CI 0.994 to 0.999) -Selenium supplements given singly decreased risk of GI cancer (RR 0.59, 95%CI: 0.46-0.75)
Dennert *et al.,* 2011 (17)	5 studies	Selenium and stomach cancer. Primary outcome measures: incidence of any cancer and cancer-related mortality	-OR 0.66 (95%CI: 0.43-1.01) -After gender stratification: non-significant
Lee *et al.,* 2011 (12)	7 RCTs	Selenium and GI cancer risk (main outcome = cancer incidence).	-Significantly reduced risk of GI cancers -RR 0.63 (95%CI: 0.46-0.88)
Myung *et al.,* 2010 (13)	8 RCTs (5 for esophageal, 3 for stomach)	Antioxidant supplements on GI cancer incidence.	-For esophageal cancer, RR 1.01 (95%CI:0.81-1.26) -For stomach cancer, RR 0.99 (95%CI: 0.76-1.24)
Psaltopoulou *et al.,* 2011 (22)	8 studies	Olive oil and GI cancer risk	-log OR for risk of GI cancer was -0.36 (95%CI: -0.50 to -0.21)
Breast Cancer			
Aune *et al*., 2012 (23)	25 prospective studies (963,885 participants)	The association between dietary intake or blood concentrations of carotenoids and breast cancer incidence	-No association between dietary carotenoid intake and breast cancer -For beta-carotene intake and breast cancer incidence, the RR for high compared to low intake was 0.93 (95%CI: 0.88,0.98) -The RR for high vs. low blood

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			concentrations of carotenoids was 0.74 (95%CI: 0.57, 0.96) -Blood concentrations of beta-carotene, alpha-carotene, and lutein were associated with a reduction in breast cancer risk
Fulan *et al*., 2011 (24)	51 studies (38 case-control, 1 case-cohort, 9 cohort, 3 RCTs)	Retinol and vitamins ACE on breast cancer risk.	-Found significantly reduced risk of breast cancer associated with total retinol intake, dietary and total vitamin A intake, dietary and total vitamin C, dietary and total vitamin E (P<0.05 for all) -No significant dose-response relationship for vitamins ACE -Results most compelling for retinol and vitamin A due to poor study design of other studies
Dennert *et al.,* 2011 (17)	7 studies	Selenium and female breast cancer incidence.	-OR 1.00 (95%CI:0.78-1.29)
Psaltopoulou *et al.,* 2011 (22)	5 studies	Olive oil and breast cancer risk	-log OR for breast cancer risk was-0.45 (95%CI: -0.78 to -0.12)
Other/Overall Cancers			
Amaral *et al*., 2010 (25)	7 case-control/case-cohort studies (1,910 cases, 17,339 controls/cohorts)	Selenium and bladder cancer risk	- The overall OR of bladder cancer risk for the highest vs. lowest selenium status was 0.61 (95% CI, 0.42-0.87) -When stratified by gender, only women had a significant decrease in bladder cancer risk with higher selenium status (OR = 0.55; 95% CI, 0.32-0.95)
Bandera *et al*., 2009 (26)	17 articles (1 RCT, 2 cohort, 12 case-control) 17804 participants	Antioxidants and endometrial cancer risk	- For dietary beta-carotene and endometrial cancer risk, the pooled OR was 0.88 (95%CI: 0.79-0.98) -For studies on dietary vitamin C intake, the pooled OR for endometrial cancer risk was 0.85 (95%CI: 0.73-0.98) - For studies on dietary vitamin E intake, the pooled OR for endometrial cancer risk was 0.91 (95%CI: 0.84-0.99)
Myung *et al*., 2011 (27)	22 case-control studies (10,073 participants)	Cervical neoplasm risk and vitamin/ antioxidant intake or serum levels. Did meta-analysis by type of vitamin or antioxidant, type of neoplasm (Cervical intraepithelial neoplasia vs. invasive cancer)	-Meta-analysis of vitamin type showed significant preventative effects for vitamins C, E, and beta-carotene (non-significant for vitamin A and selenium) -For cancer type: vitamins C and E, significantly reduced risk of CIN while vitamin C was associated with decreased risk of invasive cancer -When adjusted for HPV infection, only vitamins C and E had a significant protective effect
Dennert *et*	49 prospective	Selenium and cancer.	-Found slightly reduced risk of

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al., 2011 (17)	observational studies and 6 RCTs (18,450 participants)	Primary outcome measures: incidence of any cancer and cancer-related mortality	cancer (OR= 0.69) and cancer-related mortality (OR=0.55) with higher selenium status. However these findings are limited by study design
Lee *et al.,* 2011 (12)	9 RCTs (152,538 subjects total: 32,110 in supplement groups, 120,428 placebo)	Selenium and cancer risk (main outcome = cancer incidence). Subgroup analysis included baseline serum Se levels, high-risk vs. general population, type of cancer prevention (ie. patients without history of cancer vs. remission), and type of cancer	- Meta-analysis of all 9 trials showed that selenium supplementation significantly lowered the risk of cancer (RR 0.76; 95% CI, 0.58-0.99) - In patients with lower baseline serum Se, a greater protective effect for Se supplementation was seen (RR 0.64; 95% CI, 0.53-0.78) - When comparing patients without a history of cancer to cancer survivors, there was no observed difference when supplemented with Se
Myung *et al.,* 2010 (13)	22 RCTs (161 045 total subjects, 88 610 in supplement groups and 72 435 in placebo groups)	Antioxidant supplements (vitamins A, C, E, and selenium) on cancer incidence.	-Overall, supplementation with antioxidants had no significant effect on cancer incidence rates (RR=0.99)
Jeon *et al.,* 2011 (16)	6 RCTs (20,290 patients in supplement and 20,254 placebo groups)	Beta-carotene on cancer prevention. Primary outcome: total cancer incidence and mortality	-Beta-carotene supplementation had no significant effect on the incidence of cancer compared to the control group (RR 1.08; 95%CI, 0.99–1.18) -Beta-carotene supplementation did not reduce total cancer mortality (RR 1.00; 95%CI, 0.87–1.15) -No significant effect on type of prevention (1° or 2°)
Psaltopoulou *et al.,* 2011 (22)	38 studies (3 prospective, 35 case controls)	Olive oil and cancer risk (by cancer type) Olive oil= phenolic antioxidants NOTE: it is unclear whether or not positive results can be attributed to antioxidant or fatty acid components	-The Log OR for combined cancer risk was -0.41 (95%CI:-0.53 to -0.29)

*OR: odds ratio; RR: relative risk; CI: confidence interval; RCT: randomized control trial

Summary of Table 2:

Colorectal Cancer

There is no apparent effect of supplemental antioxidants on the risk of colorectal cancer (the majority of meta-analyses reported non-significant effects). However, there is evidence of an inverse relationship between dietary vitamins C and E and risk of colon cancer. Two meta-analyses also reported an inverse relationship between selenium status and risk of colorectal cancer. This suggests that antioxidant deficiency is a more important predictor of colorectal cancer than supplemental antioxidant intake.

Prostate Cancer

The majority of the evidence suggests that there is no effect of antioxidant supplements on risk of prostate cancer. One meta-analysis reported significant beneficial effects of dietary

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selenium intake on prostate cancer however this effect was not seen when looking at supplemental selenium.

Lung Cancer
The majority of the evidence suggests that there is no effect of antioxidant supplements on risk of lung cancer. Two large reviews of observational studies reported an inverse association between antioxidant (selenium and vitamin A) status and lung cancer incidence. One meta-analysis reported a decreased in lung cancer mortality among patients taking an antioxidant supplement containing vitamins A, C, E, and selenium. Finally, one meta-analysis reported detrimental effects of beta-carotene supplementation on lung cancer risk in smokers and asbestos workers only (non-significant among entire population). This evidence is not strong enough to implicate the use of antioxidant supplements for prevention of lung cancer however smokers and asbestos workers should never consume beta-carotene supplements as it can significantly increase their already high risk of developing lung cancer.
Gastrointestinal Cancers
There is some evidence to suggest a protective effect of selenium on GI cancer risk. Two meta-analyses reported significantly decreased risk of GI cancers associated with selenium supplementation.
Breast Cancer
There is some evidence to suggest a beneficial effect of vitamin A and beta-carotene supplementation on breast cancer risk. One meta-analysis reported a significant inverse association between beta-carotene supplementation and breast cancer risk (non-significant for dietary beta-carotene). Another meta-analysis found a significant protective effect of vitamin A and retinol on breast cancer risk when looking at both dietary intake alone and intake from supplements.
Other/Overall Cancers
Significant protective effects were reported for selenium status and bladder cancer risk, all dietary antioxidants and endometrial cancer risk, and vitamins C and E intake on cervical cancer risk. Overall, two meta-analysis reported a significant protective effect of selenium (both dietary and supplemental) on overall cancer risk.

On the whole, the evidence is strongest for a beneficial effect from selenium supplementation in certain types of cancer (lung, prostate, GI, colorectal, bladder) as well as overall cancer risk. Results for other antioxidants are conflicting and vary based on study type. Observational studies on dietary antioxidant intake show a correlation between high intake and low risk of cancer whereas RCTs on supplemental antioxidants have more conflicting results. The above evidence is not enough to call for the use of antioxidant supplements for treatment or prevention of cancer.

2.2. Hospitalized patients (including nutritional support, ICU)

Oxidative stress can be present in hospitalized patients due to underlying disease and lower antioxidant status from reduced dietary intake and increased gastrointestinal losses. It is particularly associated with patients in the intensive care unit (ICU). Critical illnesses are often associated with a state of oxidative stress which in turn can lead to mitochondrial dysfunction, systemic inflammatory response syndrome, and multi-organ dysfunction syndrome (28). In hospitalized patients, antioxidants can improve outcome by helping to reduce oxidative stress. As patients who are the most seriously ill likely have the largest depletion of antioxidants, their positive effects are most dramatic in this population. In randomised control trials of ICU patients with high mortality rates in the control group (>10%), it was found that the mortality rate was significantly lowered in the groups treated

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with antioxidant supplements (RR 0.79, 95% CI 0.68 to 0.92). This meta-analysis also found that selenium, when administered as a monotherapy reduced the rate of infection as well as the mortality rate (28).
Lipid peroxidation can also be present in patients receiving parenteral nutrition, depending on the type of lipid emulsion administered. Many factors can contribute to the stability of lipid emulsions including the manufacturing process, fatty acid composition, the emulsifier used, temperature, pH, light exposure, macronutrient concentration, cation concentration, length of infusion time, and the length of time the lipid is in the admixture (29). Lipid emulsion composition is an important factor when considering lipid peroxidation. High concentrations of polyunsaturated fatty acids (PUFAs) are more susceptible to lipid peroxidation compared to monounsaturated fatty acids (MUFAs) since double bonds are more susceptible to oxidation (30). This is one reason why olive oil based emulsions are superior to soybean oil and MCT/LCT emulsions in this respect. Lipid emulsions are also supplemented with antioxidants in the form of vitamin E in order to prevent lipid peroxidation before administration (**Table 3**) (30). Olive/soy emulsions are the most stable as they have a low proportion of PUFAs and are naturally high in vitamin E (30). Since patients on total parenteral nutrition (TPN) are often facing other types of oxidative stress due to underlying disease and poor intake or malabsorption, ensuring proper intake of antioxidants is crucial. ESPEN currently recommends that patients in intensive care on parenteral nutrition receive a daily dose of multivitamins and trace elements via a commercial multivitamin preparation (31).

Table 3: Antioxidant and fat composition of some lipid emulsions

Lipid Source	α-tocopherol (mg/L)	Fat Composition
Soybean	38	61% PUFA 26% MUFA
Soybean (50%) Safflower (50%)	28.6	69% PUFA 18% MUFA
Olive (80%) Soybean (20%)	32	22% PUFA 76% MUFA
Soybean (30%) MCT(30%) Olive (25%) Fish (15%)	200	27% PUFA 37% MUFA
Fish	150-296	42% PUFA 13% MUFA

2.3. Cardiovascular Disease

Cardiovascular disease (CVD) is among the leading causes of death due in part, to the high prevalence of obesity and metabolic syndrome. Atherosclerosis is one of the main causes of CVD and involves lipid peroxidation. Oxidation of LDL in the vessel endothelium causes inflammation and recruitment of macrophages. The oxidized LDL is taken up by the macrophages, causing them to become foam cells which contribute to plaque formation.
Vitamin E, an important antioxidant in preventing lipid peroxidation, has been shown to reduce the risk of myocardial infarction (32). Another meta-analysis on the relationship between antioxidant enzyme activity and coronary hearth disease found a significantly reduced risk of coronary heart disease associated with a significant increase in GPx acitivity

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(OR 0.51; 95%CI 0.35-0.75). This study also saw similar results for the antioxidant enzymes SOD and catalase (33).
However, there is controversy about using vitamin E supplementation as previous studies have shown an association between vitamin E supplementation ≥400IU/day and increase in all-cause mortality (34,35). More research needs to be done to determine if the discordant data can be attributed to varying doses as often the doses of vitamin E administered are extremely high.

2.4. Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is characterized by the build-up of fat in the liver, in the absence of excess alcohol consumption (< 20 g/day). NAFLD is a spectrum of histological findings from steatosis to non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis, which can eventually lead to cirrhosis. The cause for progression of NAFLD is still not fully understand but is associated with multiple mechanisms which include the presence of insulin resistance, lipolysis and increased free fatty acid uptake in the liver associated with reduced mitochondrial beta-oxidation, VLDL secretion and increased de novo lipogenesis. The accumulation of free fatty acids will predispose to lipid peroxidation, which in turn, will contribute to the release of inflammatory cytokines. This, along with the contribution of other factors such as adipokines, reduced adiponectin, intestinal microbiota and diet, will cause NASH (36).
Studies on antioxidant supplementation in patients with NAFLD have shown improvement in several NAFLD-related outcomes including improvement in liver enzymes (36), as well as lobular inflammation and steatosis progression (37). In both of these meta-analyses, vitamin E was found to be the causative agent of the observed improvements.

2.5. Smoking and Lung Disease

Smokers have a very high risk of oxidative damage to the lungs which increases their risk of lung cancer or other lung diseases such as chronic obstructive pulmonary disease (COPD). Cigarette smoke contains thousands of chemicals including many free-radicals and pro-oxidants. In the lungs, the oxidative burden of smoking can be amplified by the release of oxygen radicals from neutrophils and macrophages which are recruited to the lungs to deal with damage from smoking.
Since smokers face severe oxidative stress, the recommended daily allowance (RDA) of vitamin C in smokers is higher to deal with the effects. Studies have also shown evidence for a protective effect of selenium and vitamin A (retinoids) on lung cancer. However, beta-carotene has been shown to promote lung cancer in smokers due to its pro-oxidant effects at high oxygen pressures.
In a study on vitamin intake levels and COPD, it was shown that patients with higher dietary intakes of antioxidant vitamins showed more improvement in spirometric values. However, no effect was seen in patients receiving additional vitamin supplements.
Several meta-analyses have shown results supporting antioxidant supplements in patients with asthma. Improvements were seen in asthma outcome, severity, and wheeze (38) as well as forced expiratory volume (FEV) (39) with antioxidant vitamin intake. In stratification by vitamin type, vitamin A showed the most compelling results for most outcomes (incidence, severity, and wheeze) (38) while vitamin C was found to be attributed to improvement in FEV (39).

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2.6. Aging and Dementia

Elderly populations are at higher risk for nutritional deficiencies due to several factors which include aging process, underlying diseases, poly-pharmacy, socio-economic issues and disability leading to reduced activity levels (e.g. difficulty buying and preparing food) and sedentary lifestyle. This, in addition to low dietary and micronutrient intake may weakened the antioxidant status and increase the risk of certain diseases associated with oxidative stress. In addition, the free radical theory of aging suggests that organisms age due to cellular accumulation of free radical damage over time. Studies investigating the effects of supplemental antioxidants on prolonging lifespan in both humans and model organisms have shown inconsistent results.

Meta-analysis on the effects of antioxidant supplements in humans have shown a protective effect for vitamin E and vitamin C on development of Alzheimer's dementia (AD), with the most compelling evidence for the use of vitamin E (40) (41). The tissue of the central nervous system is largely composed of lipids, which is susceptible to lipid oxidation by pro-oxidants, causing damage that could lead to cognitive impairment. Since vitamin E is fat-soluble and can cross the blood-brain barrier, it is of particular importance in the study of AD.

2.7. Cataract and Macular Degeneration

Photoreceptors of the eye are highly susceptible to oxidative damage due to exposure to both light and oxygen. This damage can accumulate and lead to injury in the form of cataract or macular degeneration. Age-related macular degeneration (AMD) is a condition in which the central field of vision is lost due to lipid deposits in the retina. This condition is age-related and occurs almost exclusively in the elderly population. Cataract is characterized by clouding of the lens of the eye. This occurs when clear proteins in the lens of the eye denature, which can be caused by oxidative protein damage. Cataract is also often age-related, supporting the free radical theory of aging.

Research on the effects of antioxidant supplementation on cataract and AMD has been promising. Two meta-analyses have shown significant results for the slowing of the progression of AMD due to antioxidant supplementation (42)(43). Antioxidant supplementation with vitamin E, C, and β-carotene has also been shown to slow down the progression of cataract (43). Nevertheless, there is no convincing evidence that antioxidants have a role in prevention of these two pathologies.

3. Summary

Antioxidants are important to reduce the burden of oxidative stress on the body. Antioxidants are ingested in the diet and can also be produced endogenously in the body. Dietary antioxidants are predominantly the form of vitamin A, vitamin C, vitamin E, and selenium.

Oxidative damage to DNA, proteins, and lipids can lead to a wide variety of diseases including cancer, CVD, NAFLD, lung disease, dementia, cataract, and macular degeneration. Thus, it is important to maintain intake of dietary antioxidants to minimize disease risk.

Meta-analyses of studies on the effects of non-dietary antioxidants on various diseases have shown conflicting results, however it is generally agreed upon that antioxidant supplementation, with a few important exceptions (e.g. carotenoids and lung cancer, vitamin E and prostate cancer), is unlikely to cause harmful effects and may occasionally be beneficial provided appropriate dosage is administered. Beneficial effects have been observed for selenium in cancer; antioxidant supplementation in ICU patients; vitamin E in

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CVD; vitamin E in NAFLD; antioxidants in asthma; vitamin E in Alzheimer's dementia; and antioxidants in cataract and macular degeneration.

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