

## The effect of red and white wine consumption on breast cancer risk in women

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### Abstract

Cancer is a severe group of diseases caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) Breast cancer is currently the most common invasive cancer in women. Our goal is to decrease the risk of this disease through proper diet and lifestyle. The purpose of this study is to determine if a natural substance from red wine which is almost absent in white wine, called resveratrol, has the ability to influence the circulating blood estrogen level, influencing one of the many risk factors of breast cancer (estrogen blood level) despite the disadvantage that it contains alcohol which already represents an independent risk factor. Method: We have made a parallel-group randomized controlled trial to which 70 women attended, for three month. The two groups were randomly split 38 for the red wine, 32 women for the white wine, because natural Resveratrol content in wine interferes with all three stages of carcinogenesis—initiation, promotion and progression. Results: 31 women from the red wine group and 27 from the white wine group finished the trial successfully. In conclusion although this study did not prove that 150 ml daily intake of neither red wine or white wine for 2 months could influence the estrogen levels of premenopausal women, we will continue the research to influence the risk of later developing breast cancer.

**Keywords:** breast cancer, risk factors, nutrients, health, resveratrol

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### 1. Introduction

Cancer is a severe group of diseases that cause cells in the body to change and grow out of control. Most types of cancer cells eventually form a lump or mass called a tumor, and are named after the part of the body where the tumor originates [1]. If the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) [2]. Breast cancer is currently the most common invasive cancer in women. It occurs in humans and other

mammals. More than 99% of the cases it occurs on women [3]. Worldwide, breast cancer accounts for 22.9% of invasive female cancers and 16% of all cancers in women [4]. In 2008, breast cancer caused 13.7% of cancer deaths in women [5]. Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment, and geographical location of the patient [6]. Between the several grading systems, receptor status to estrogen has predictive value of response to hormonal therapy.

The three major naturally occurring estrogens in women are estrone, estradiol, and estril. Estradiol is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in

terms of estrogenic activity [7]. During menopause, estrone is the predominant circulating estrogen and during pregnancy estriol is the predominant circulating estrogen in terms of serum levels [8]. In females, synthesis of estrogens starts in theca interna cells in the ovary, by the synthesis of androstenedione from cholesterol. Androstenedione is a substance of weak androgenic activity which serves predominantly as a precursor for more potent androgens such as testosterone as well as estrogen. This compound is converted either immediately into estrone, or into testosterone and then estradiol in an additional step. The conversion of androstenedione is made in two ways: to testosterone alone or androstenedione and testosterone into estrone and estradiol which is catalyzed by aromatase [37].

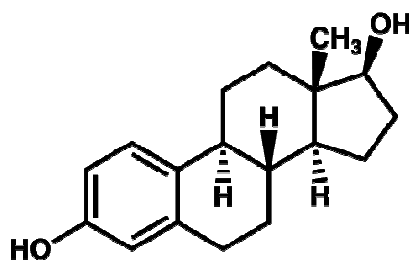


Figure 1. Estradiol

The menstrual cycle has three phases: the follicular phase, the ovulation, the luteal phase. The estradiol level has fluctuations during this cycle, with values rising more than 3 times from the early follicular phase to the LH peak (ovulation) [45].

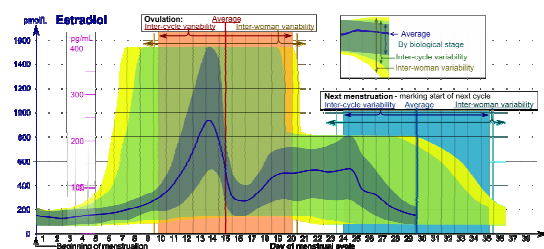


Figure 2. Estradiol in the menstrual cycle

There are two major receptors for estrogen of the nuclear hormone receptor family, ER $\alpha$  and ER $\beta$ . The majority of breast cancers about 70% express the estrogen receptor ER $\alpha$  which has been developed clinically as classifier of breast cancers that respond to hormonal therapy [9]. ER $\alpha$  can be targeted with selective estrogen receptor

modulators (SERMs) that competes with estrogen and alter the conformation of the ligand-binding domain of the receptor or aromatase inhibitors [10].

Estrogen plays a crucial role in the development of breast cancer, and the inhibition of estrogen synthesis has been an important target for the prevention and treatment of this disease. The rate-limiting reaction of the hormone biosynthesis is catalyzed by cytochrome P450 (CYP) 19 enzyme or aromatase. It has been of genuine interest to uncover an aromatase-inhibitory compound from a dietary source. Resveratrol is a polyphenolic compound that can be isolated from grape peel. Because of its structural resemblance to estrogen, resveratrol's agonistic and antagonistic properties on estrogen receptor have been examined and demonstrated [11,31,32].

Wine is an alcoholic beverage made from fermented grapes. Wine is usually made from one or more varieties of the European species *Vitis Vinifera* [12]. The color of the wine mainly depends on the color of the drupe of the grape variety. White wines are being produced by removing the skins immediately after picking [13].

Resveratrol has been shown to have chemoprotective effects in animal studies [14]. Resveratrol is produced naturally by grape skins in response to fungal infection, including exposure to yeast during fermentation. As white wine has minimal contact with grape skins during this process, it generally contains lower levels of the chemical. It exists as two geometric isomers: *cis*- and *trans*-[36]. In red wine, the concentrations of the *trans*-isomer, which is the major form, generally ranges between 0.1 and 15 mg/L [15].

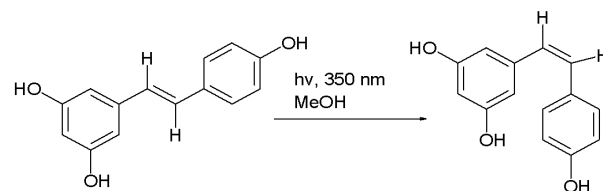


Figure 3. Resveratrol exists as two geometric isomers *cis*- and *trans*

Resveratrol interferes with all three stages of carcinogenesis—initiation, promotion and progression. Experiments in cell cultures of varied types and isolated subcellular systems in vitro imply many mechanisms in the pharmacological activity of

resveratrol. These mechanisms include modulation of the transcription factor NF- $\kappa$ B [17], inhibition of the cytochrome P450 isoenzyme CYP1A1 [18] (although this may not be relevant to the CYP1A1-mediated bioactivation of the procarcinogen benzopyrene [19], alterations in androgenic actions [20] and expression and activity of cyclooxygenase (COX) enzymes. In vitro, resveratrol "inhibited the proliferation of human pancreatic cancer cell lines." In some lineages of cancer cell culture, resveratrol has been shown to induce apoptosis, which means it kills cells and may kill cancer cells [20,21,22,23,24,25]. It has been shown to induce Fas ligand mediated apoptosis, p53 and cyclins A, B1, and cyclin-dependent kinases cdk 1 and 2. It also possesses antioxidant and anti-angiogenic properties [26,27,28] and it significantly increases natural testosterone production from being both a selective estrogen receptor modulator [29,30,31,32,33] and an aromatase inhibitor [34,35].

## 2. Materials and method

We have made a parallel-group randomized controlled trial to which 70 women attended. All were in general good health, of minimum age 18, pre-menopausal women with regular ovulatory cycles for 12 months prior to the study, with a BMI of 18.5-35, on regular, unrestricted diet, not within the last 3 months and currently using oral contraceptives or other hormone replacement therapy. The two groups were randomly split 38 for the red wine, 32 women for the white wine. The red wine group was given a certain type of local, under 1 year old harvest, no wood (oak) aged, red wine (Cabernet Sauvignon) known to have a thick skin (a higher percentage of resveratrol), with an alcohol level of 12,5%. The white wine group was given Sauvignon Blanc, under 1 year old harvest, with few traces of resveratrol, and an alcohol percentage of 10,5%. Every subject had the first month no kind of food or drink interdiction, in the second and in the third month had to drink 1 glass of 150 ml of wine (each group with its type of wine) per evening, after supper, for 2 months, and no other alcoholic beverages, grape juice, grapes or raisins. The test finished after three months.

Every woman has been tested using an Abbott Architect analyzer, the blood samples have been taken morningly, before breakfast, in the 5 (early follicular phase) and in the 22th (mid luteal) day of the cycle where the values vary less, having the smallest slope value to an anterior or a posterior day. 31 women from the red wine group and 27 from the white wine group finished the trial successfully.

## 3. Results and Discussions

The results are as follows: Tabel 1 and Table 2.

There has been no notable difference on any of the groups. Neither the red wine group or the white wine group did not obtain lower estrogen levels in any of the two constant wine consuming months. Comparing the data with other studies, Hirvonen *et al* reported no significantly increased risk of breast cancer associated with either red or white wine after a median 6.6 years follow-up in a placebo-controlled antioxidant primary-prevention trial [46]. A small case-control study of premenopausal women (n=154 cases and 154 controls) reported an increase in breast cancer for women who reported consuming more than 4 liters of red wine per month, or ~1 drink/day (OR=4.0; 95% CI 1.6–9.8; P-trend=0.003) [47]. Newcomb *et al* reported no difference between red wine and white wine consumption on breast cancer risk on a population-based case-control study in Massachusetts [53].

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**Table 1.** Red wine group

Red wine group	Month 1	Month 2	Month 3
	<i>5th/22th</i>	<i>5th/22th</i>	<i>5th/22th</i>
1.	125/504	123/514	118/490
2.	138/522	143/530	129/520
3.	138/513	137/507	134/510
4.	132/500	139/524	136/520
5.	133/478	130/505	135/508
6.	136/540	127/470	135/508
7.	145/505	138/547	124/537
8.	143/470	155/524	167/540
9.	140/498	137/480	132/450
10.	149/505	122/514	134/500
11.	136/501	140/512	150/509
12.	137/490	148/476	136/523
13.	120/488	155/492	136/523
14.	142/456	128/500	119/503
15.	122/497	150/489	144/460
16.	135/548	167/523	138/489
17.	135/488	167/523	132/538
18.	132/476	113/530	136/502
19.	134/532	139/470	123/489
20.	144/504	137/524	122/540
21.	123/502	137/524	151/534
22.	126/569	98/490	131/515
23.	128/520	123/534	136/513
24.	115/503	122/487	123/504
25.	131/501	158/540	142/499
26.	138/511	132/503	137/518
27.	117/495	139/532	125/499
28.	136/499	144/502	130/506
29.	135/476	123/507	134/511
30.	133/539	143/459	131/469
31.	133/539	112/542	138/550
<b>Mean value</b>	<b>124.4/488.4</b>	<b>130.8/491.1</b>	<b>129.5/491.5</b>

**Table 2.** White wine group

White wine group	Month 1	Month 2	Month 3
	<i>5th/22th</i>	<i>5th/22th</i>	<i>5th/22th</i>
1.	128/503	125/519	132/512
2.	113/472	117/500	112/489
3.	143/523	137/531	142/521
4.	123/489	120/494	128/499
5.	159/552	147/531	150/535
6.	131/503	137/509	127/499
7.	148/523	144/523	147/519
8.	132/477	121/469	118/479
9.	132/511	123/514	152/520
10.	114/532	113/523	126/517
11.	141/541	134/520	145/532
12.	130/504	127/499	123/516
13.	121/511	127/502	131/502
14.	135/505	139/532	127/504
15.	117/496	119/481	111/478
16.	162/542	148/518	155/539
17.	123/512	112/503	131/500
18.	173/569	187/524	177/543
19.	140/507	138/512	145/523
20.	134/477	127/472	128/480
21.	104/454	109/471	102/451
22.	132/512	123/518	136/507
23.	126/501	132/496	129/497
24.	130/505	122/505	132/479
25.	110/508	117/503	111/515
26.	144/532	148/537	143/543
27.	123/522	120/548	132/523
<b>Mean value</b>	<b>132.1/510.5</b>	<b>130.1/509.4</b>	<b>133/508.2</b>

## Discussions

Separate effects of red versus white wine on risk may have biological plausibility. Resveratrol, a polyphenol in grapes, has displayed anti-carcinogenic properties in mouse mammary cultures [48,49] and in human mammary cultures [24,30,31], antiestrogenic properties[30,31,32,33,34], aromatase inhibitor properties [34,35] but its oral bioavailability is approximately 1% due to extensive hepatic metabolization, gluconuridation and sulfation, consistent intake of two glasses of red wine daily would be equivalent to a dose of ~27 µg/kg body weight for a 70 kg individual, leading to detectable concentrations of derivatives but not free resveratrol [50,51]. To benefit fully from resveratrol in wine, it is recommended to sip slowly when drinking. Due to inactivation in the gut and liver, most of the resveratrol consumed while drinking red wine does not reach the blood circulation. However, when sipping slowly, absorption via the mucous membranes in the mouth can result in up to 100 times the blood levels of resveratrol [16]. On the other hand wine alcohol has a rising effect on the estrogen level both in pre-menopausal as in post-menopausal women. A variety of study designs have reported an alcohol-induced rise in estrogen levels [52]. This is attributed this to a side-effect of alcohol metabolism on the oxidation of oestradiol [38] or to increased aromatization of testosterone to oestradiol [39,40,41,42]. It is possible that both mechanisms may be operating [43]. According to American Cancer Society high levels of endogenous estrogen represent a relative risk of encountering breast cancer of 2,1-4 while alcohol consumption has a 1,1-2 relative risk of developing breast cancer later in lifetime [44], higher level of endogenous estrogen level having a double priority.

Red wine through resveratrol might have estrogen lowering effects and so anticarcinogenic effect but the main limitation of our technique is that patients could not be entirely monitorized concerning the diet.

## Conclusion

1. Diet and lifestyle influence the occurrence and the development of many serious diseases. By choosing the healthiest lifestyle options possible, you can empower yourself and make sure your breast cancer risk is as low as possible.

2. This research did not prove that 150 ml daily intake of neither red wine or white wine for 2 months could influence the estrogen levels of premenopausal women, and by influencing the estrogen level to influence the risk of later developing breast cancer.
3. Although this study did not prove the direct influence of natural Resveratrol content in wine on estrogens decrease we will continue research to influence the risk of later developing breast cancer.

**Compliance with Ethics Requirements:** Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest and all procedures involving human and/or animal subjects (if exists) respect the specific regulations and standards.

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