Impact of cows' milk estrogen on cancer risk

Peter W. Parodi

Human Nutrition and Health Research, Dairy Australia, Melbourne, Australia

Abstract

Estrogens have been implicated in cancer at hormone-responsive sites, such as the breast, ovaries, endometrium and prostate. Because cows' milk contains estrogens, some authors have suggested that its consumption may contribute to the risk of cancer at these sites. However, these reports do not recognize the complex mechanisms these cells possess to regulate estradiol levels. Hormone-responsive and many peripheral cells contain all the necessary steroidogenic enzymes necessary for in situ synthesis of bioactive estradiol from abundant androgenic precursors and for inactivation of unwanted estrogens. Estradiol from dairy products is extensively inactivated in the gastrointestinal tract and only about 5% survives the first pass to the liver. Thus daily dairy product intake would supply only about 0.25% of the FAO/WHO upper acceptable daily intake of estradiol. Available epidemiological evidence does not suggest an association between dairy product consumption and risk of cancer of the breast, ovaries and endometrium.

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1. Introduction

It is generally accepted that estrogens are involved in the development of cancer at hormone-responsive sites, such as the breast, ovary and endometrium and, in conjunction with testosterone, the prostate (Bernstein & Ross, 1993; Kaaks, Lukanova, & Kurzer, 2002; Lukanova & Kaaks, 2005; Risbridger, Bianco, Ellem, & McPherson, 2003). Even so, the mechanisms whereby estrogens influence carcinogenesis remain largely unresolved. A number of publications have hypothesized that estrogen present in cows’ milk may be responsible for the development of cancer in estrogen-responsive organs (Farlow, Xu, & Veenstra, 2009; Gannaia & Sato, 2005; Outwater, Nicholson, & Barnard, 1997; Qin, Wang, Kaneko, Hoshi, & Sato, 2004). However, these hypotheses fail to take into account the complex mechanisms involved in the synthesis and metabolism of estrogens within the cell and the metabolic processes associated with the absorption of exogenous estrogens. These aspects, together with a brief outline of relevant aspects of estrogen carcinogenesis, are discussed in this review.

2. Estrogens and cancer risk

2.1. Observational studies

The study of breast cancer has received more attention than cancer at the other hormone-responsive sites. Nevertheless, the causes of breast cancer are still largely undetermined. Evidence from a number of observational studies suggests that several reproductive factors, which indicate an increased exposure to estrogens, increase breast cancer risk. Early menarche, late menopause, nulliparity and first pregnancy late in life are associated with increased risk. Bilateral oophorectomy, especially at an early age, reduces risk. On the other hand, oral contraceptive use that prevents ovulation and decreases serum estrogen levels results in a slight increase in risk. In contrast, breast-feeding (particularly for long durations, which also prevents ovulation) is associated with lower risk, but this protection may result from cell differentiation (Bernstein & Ross, 1993; Chodosh et al., 1999; Harris, Lippman, Veronesi, & Willett, 1992; Kuller, 1995).

Evidence for a role of estrogens in endometrial cancer is robust and it is considered that exposure to estrogens, unopposed by progesterone, is a major etiological factor. Early menarche and late menopause are risk factors, whereas parity is protective. A low level of physical activity and obesity increase risk, possibly due to a reduction in progesterone levels. There is an increased risk of endometrial cancer in users of estrogen-only oral contraceptives and hormone replacement therapy, but no increased risk when progesterone is included in the preparation (Kaaks et al., 2002; Pike, Spicer, Dahmoush, & Press, 1993).

The cause of ovarian cancer is largely unknown. Observational evidence on the role of estrogens is conflicting and often open to alternative interpretation. There is some support for the concept that continual ovulation may predispose women to development of ovarian cancer. Pregnancy, breast-feeding and oral contraceptive use are protective, but hormone replacement therapy is associated with increased risk (Lukanova & Kaaks, 2005; Risch, 1998). Although androgens are considered to have an important role in prostate cancer development, animal and human cell culture studies now suggest a role for estrogens (Bosland, 2004; Harkonen & Makela, 2004). Recent studies with genetically modified mouse models show that malignant changes to the prostate gland are dependent on both androgen and estrogen responses, and that neither hormone alone can produce an aberrant growth pattern that leads to malignancy (Bosland, 2004; Risbridger et al., 2003).

2.2. Experimental studies and mechanisms

There is ample evidence that administration of estradiol (17β-estradiol) to laboratory animals induces tumors and that castration and use of antiestrogen drugs inhibits tumor development (Bernstein & Ross, 1993; Liehr, 2000). The mechanisms whereby estrogens cause cancer have not been established conclusively. A commonly held hypothesis is that circulating estrogens diffuse passively through cellular membranes of estrogen-responsive cells and bind to nuclear estrogen receptors (ERs) of which there are two forms, ERα and ERβ. Binding to ERs stimulates transcription of genes involved in cell proliferation. Rapidly proliferating cells are susceptible to genetic errors during DNA replication, which if uncorrected may ultimately lead to cancer. Estradiol may also increase proliferation in cells already having mutations due to other sources of DNA damage (Santen, 2002; Yager & Davidson, 2006; Yue et al., 2003).

It has also been proposed that non-receptor-mediated mutagenesis induced by oxidized estrogen metabolites may contribute to carcinogenesis (Cavalieri, Devanesan, Bosland, Badawi, & Rogan, 2002a; Cavalieri et al., 2002b; Rogan et al., 2003; Yager & Davidson, 2006). Estrogen metabolites are formed by a series of oxidative biotransformations, both in the liver and in extrahepatic estrogen-responsive organs by the activities of a series of cytochrome P450 enzymes. There are two major mutually exclusive pathways for the transformation of estradiol and estrone. In the first pathway the A ring is hydroxylated at position 2 or 4 to produce the catechol estrogens 2-hydroxyestradiol and 2-hydroxyestrone or 4-hydroxyestradiol and 4-hydroxyestrone, respectively. These four metabolites may be inactivated in the liver and extrahepatic estrogen-responsive tissue by glucuronidation and sulfation and particularly in extrahepatic tissues by the enzyme catechol-O-methyltransferase (COMT), which forms 2- and 4-methoxyestriadiols, and methoxyestrone. In certain conditions catechol estrogens may be oxidized further to reactive catechol estrogen semiquinones then to catechol estrogen-2,3-quinones and catechol estrogen-3,4-quinones. Protection against the catechol estrogen-quinones occurs through conjugation with glutathione catalyzed by glutathione-S-transferases. Another protection mechanism results when catechol estrogen-quinones are re-cycled to catechol estrogens by the action of quinone reductases (Cavalieri, Frenkel, Liehr, Rogan, & Roy, 2000; Lakhani, Sarkar, Venitz, & Figg, 2003; Yue et al., 2006). The second major oxidation pathway occurs at the D ring with the formation of 16α-hydroxyestradiol and 16α-hydroxyestrone. These 16α-hydroxyderivatives may be further oxidized to estriol (Clemens & Goss, 2001; Mueck, Seeger, & Lippert, 2002).

Estrogenic and genotoxic properties of the various estrogen metabolites vary from one and other and from their parent estrogens. For instance, the 2-hydroxyestrogens bind to ERs with affinity comparable with that for estradiol, but have limited mitogenic effect and are considered antiestrogenic and anticarcinogenic (Bradlow, Telang, Sepkovic, & Osborne, 1996; Mueck et al., 2002). 2-Methoxyestradiol has very low affinity for ERs, but exhibits potent apoptotic activity against rapidly growing cancer cells, possesses antiangiogenic properties and has been tried on patients with breast and prostate cancer (Lakhani et al., 2003). On the other hand, 16α-hydroxyestradiols that bind to ERs with lower affinity than estradiol are thought to have a carcinogenic influence (Mueck et al., 2002).

Attention has focused on the estrogen-2,3- and estrogen-3,4-quinones because of their ability to act both as electrophiles and oxidants. As electrophiles, catechol quinones can form covalent adducts with the purine bases adenine and guanine of DNA, these depurinating adducts generate apurinic sites that may lead to mutations and in turn cancer. As oxidants, catechol quinines redox
cycle with their semiquinones, producing the superoxide anion and reactive oxygen species that may damage lipids and DNA (Cavaliere et al., 2000; Yager & Davidson, 2006). The proposed ER- and non-ER-mediated pathways may act in concert in an additive or synergistic manner to cause cancer (Yue et al., 2003). However, under normal physiological conditions deactivation and conjugation processes should ensure that insufficient reactive quinines are produced to cause significant DNA damage, whereas normal cellular antioxidants should prevent oxidative damage. High levels of hydroxy- and methoxyestrogens are found in blood (Elíasen, Mismmer, Tworoger, & Hankinson, 2008) and urine (Elíasen et al., 2009). Indeed, hydroxy- and methoxyestrogens can represent up to 95% of the total estrogens in normal breast tissue (Castagnetta et al., 2002; Rogan et al., 2003). Overall, no studies have demonstrated that estrogen metabolites contribute to cancer in humans (Yager & Davidson, 2006).

3. Serum estrogen levels and the risk of cancer

Many studies have examined the associations between circulating estrogen levels and the risk of breast, endometrial, ovarian and prostate cancer. Because these cancers produce estrogens during their development only studies where blood was drawn prospectively will be considered here. Estradiol circulates bound to carrier proteins with around 70% bound to sex hormone-binding globulin (SHBG), which inhibits its bioactivity, and 30% is more loosely bound to albumin. Only about 1% circulates in the free form (Grow, 2002). Elíasen and Hankinson (2008) recently reviewed sieroepidemiological studies of breast, endometrial and ovarian cancer, and the Endogenous Hormones and Prostate Cancer Collaborative Group (2008) conducted a pooled analysis of 18 prospective studies, which examined the associations between sex hormone concentrations and the risk of prostate cancer.

3.1. Breast cancer

The Endogenous Hormones and Breast Cancer Collaborative Group (2002) analyzed data from nine prospective studies of 663 postmenopausal women who developed breast cancer. The relative risk (RR) with 95% confidence intervals (CI) for the highest compared with the lowest quintile of serum estradiol, free estradiol, estrone and estrone sulfate was 2.00 (1.47–2.71), 2.58 (1.76–3.78), 2.19 (1.48–3.22) and 2.00 (1.26–3.16), respectively. For SHBG, the RR was 0.66 (0.43–1.00). Since this analysis, results for combined data from the Swedish Malmo Diet and Cancer Study (MDCS) and the Northern Sweden Health and Disease Study (NSHDS), the New York University Women’s Health Study (NUSWHS), the Nurses’ Health Study (NHS), and the European Prospective Investigation into Cancer and Nutrition (EPIC), were reported and are reviewed by Elíasen and Hankinson (2008). Results from the Studies of Hormones and Diet in the Etiology of Breast Tumors (ORDET) were recently reported (Sieri et al., 2009). In all these studies, there was roughly a two-fold increase in risk of breast cancer with elevated levels of estrogens.

Only a few studies have reported associations between circulating estrogens and the risk of premenopausal breast cancer. This is undoubtedly due to the difficulty in obtaining a representative sample for menstruating women. Five small studies found no association between estrogen levels and the risk of breast cancer. Results from two recent large studies indicate that in the EPIC cohort there was no association between estradiol or estrone levels and the risk of breast cancer. On the other hand, in NHS II there was a significant positive association between breast cancer risk and estradiol levels in blood collected during the follicular phase, but not for luteal estradiol. There was no association between follicular or luteal estrone levels and the risk of breast cancer (Elíasen & Hankinson, 2008).

Two prospective studies found positive associations between urinary estrogen levels and risk of postmenopausal breast cancer (Key et al., 1996; Onland-Moret et al., 2003). However, the relevance of urinary estrogens to functions in target cells is uncertain. Seven prospective studies examined associations between either serum or urinary estrogen metabolites and risk of breast cancer in both pre- and postmenopausal women. These studies measured only 2-hydroxysterone and 16α-hydroxysterone and overall there were no statistically significant associations between these two metabolites or the ratio of 2-hydroxysterone: 16α-hydroxysterone and the risk of breast cancer (Arslan et al., 2009; Elíasen, Mismmer, Tworoger, & Hankinson, 2008).

3.2. Endometrial cancer

There has been only one large prospective study on circulating sex hormone levels and the risk of endometrial cancer (Lukanova et al., 2004). This study combined data for postmenopausal women from the NYUWHS, ORDET and NSHDS cohorts. Estradiol and estrone levels were strongly associated with endometrial cancer risk with RRs of 4.13 (1.76–9.72) and 3.67 (1.71–7.88), respectively. SHBG was negatively associated with risk of endometrial cancer, RR 0.46 (0.02–1.05).

3.3. Ovarian cancer

Elíasen and Hankinson (2008) reviewed the few prospective studies that investigated associations between serum sex hormone concentrations and the risk of ovarian cancer. Overall, there is no convincing evidence for an association between circulating levels of estrogens or androgens and the risk of ovarian cancer in pre- or postmenopausal women.

3.4. Prostate cancer

The Endogenous Hormones and Prostate Cancer Collaborative Group (2008) conducted a collaborative analysis of worldwide data from 18 cohort studies that investigated the association between endogenous hormone concentrations and the risk of prostate cancer in 3886 men with incident prostate cancer and 6438 control subjects. There were no statistical significant associations between serum concentrations of any androgens or estradiol and the risk of prostate cancer. For estradiol the RR for the highest versus lowest level of estradiol was 0.93 (0.77–1.11) and 0.95 (0.79–1.15) for free estradiol. An investigation of the possibility that a combination of estrogens and androgens may be more strongly associated with the risk of prostate cancer than either estrogen or androgen alone, found no evidence of any interaction.

4. Relationship between circulating estrogen levels and levels in breast tissue

To date, the strongest consistent evidence for a role of circulating estrogens in cancer is for postmenopausal breast cancer. However, circulating hormone levels may not reflect hormone concentrations in target cells. Even so, epidemiological associations cannot be used to ascribe causality and improved knowledge of estrogen metabolism at the cellular level is required.

Several studies have compared estrogen levels in normal and malignant breast tissue with the levels in blood from pre- and postmenopausal women (Cherite, Cortes-Prieto, Philippe, Wright, & Pasqualini, 2000; Geisler, 2003; van Landeghem, Poortman, Nabuurs, & Thijssen, 1985; Pasqualini et al., 1996; Thijssen, van...
Landeghem, & Poortman, 1986). Even though serum estrogen levels are up to 50-fold lower in postmenopausal than in premenopausal women, their unconjugated estrogen levels in normal and malignant breast tissue are similar. Estradiol levels are some 2.5-fold higher in breast cancer tissue than in normal tissue for both pre- and postmenopausal women. In breast cancer tissue estradiol levels are about 10- to 20-fold higher and estrone levels 2- to 10-fold higher than their corresponding serum levels. Available studies suggest there is no simple correlation between the levels of estrogens in serum and their level in tissue. These data suggest that postmenopausal breast tissue has the ability to selectively accumulate estrogens from the circulation or to synthesize them within the tissue.

5. Relationship between urinary estrogens and estrogen metabolites in breast tissue

Only one study was found that compared the levels of estrogens and estrogen metabolites in breast tissue with those in urine. In a small study, Taioli et al. (2010) found that total estrogen metabolite levels were similar between breast tissue and urine. However, the levels of individual components were quite different between the two sources. The sum of estrone and estradiol was significantly higher in breast tissue than urine, while the metabolites of the 2- and the 16-hydroxylation pathways were lower, the latter significantly lower. The ratio of 2:16 hydroxylation products was nonsignificantly higher in breast tissue than in urine. There were large inter-individual variations in tissue to urine ratios of estrogens and their metabolites. It is possible that not all urinary estrogens and their derivatives originated from breast tissue.

6. Formation and transformation of tissue estrogen levels in the breast and other estrogen-responsive tissues

There is now substantial evidence that normal and malignant breast tissue contains all the necessary steroidogenic enzymes necessary for the synthesis of estradiol from circulating inactive androgenic precursors (Labrie, 2003; Labrie et al., 2003; Pasqualini, 2004; Perel, Wilkins, & Killinger, 1980). Dehydroepiandrosterone (DHEA) sulfate (S) is by far the predominant adrenal-derived circulating precursor hormone in men and women. Its concentration is from 1000 to 10,000 times higher than that of estradiol and 100–500 times higher than that of testosterone. There is also considerable estrogen sulfate and lesser amounts of androstenedione and androstenediol in serum. Initially, DHEA-S is converted to DHEA by the enzyme steroid sulfatase (Fig. 1). DHEA can then take part in two pathways. Reduction by members of the 17β-hydroxysteroid dehydrogenase (17β-HSD) family produces
androstenediol (17β-HSD types 1,3,5 and 7 are involved in reduction reactions, whereas 17β-HSD types 2,4 and 6 are involved in oxidation reactions). The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) converts both DHEA and androstenediol to androstenedione and testosterone, respectively, which, in turn, are converted to estrone and estradiol by the aromatase enzyme. The DHEA → androstenediol, androstenedione → testosterone and estrone → estradiol conversions are interconvertable, depending on the oxidative/reductive forms of 17β-HSD available, but the action of aromatase is irreversible. Estrone and estradiol may also be formed by the action of steroid sulfatase on estrone sulfate and estradiol sulfate, respectively.

Although not studied to the same extent as breast tissue, endometrial and ovarian tissue also contain a range of steroidogenic enzymes capable of synthesizing estrogens from circulating precursors (Ito, Utsunomiya, Yaegashi, & Sasano, 2007; Sasano & Harada, 1998). The prostate likewise possesses all the necessary enzymes to convert circulating DHEA into estradiol and testosterone, as well as 5α-reductase to convert testosterone to the more bioactive dihydrotestosterone (Takase et al., 2006). Normal cells possess mechanisms to ensure estradiol hormone-stasis. ER expression in normal breast epithelial cells is inversely related to circulating estradiol levels (Chetrite et al., 1999; Soderqvist, von Schoultz, Tani, & Skog, 1993). Estrone and estradiol can be converted to inactive sulfates by the action of steroid sulfotransferase and either excreted from the cell or retained for future supply of estrone and estradiol. Conjugation of estrone and estradiol by uridine diphosphate-glucuronosyltransferases inactivates and produces the more soluble estrogen glucuronides that are excreted to bile and urine. O-methylation of hydroxysterogens by COMT and conjugation of estrogen quinones with glutathione facilitates removal of estrogen metabolites from cells.

The expression and level of the various steroidogenic and metabolizing enzymes in each cell of hormone-responsive tissues may influence their estrogen content and potential to transform. For instance, a higher activity of the reducing forms of 17β-HSD may lead to higher levels of estradiol. Aromatase is important for the conversion of androstenedione to estrone and testosterone to estradiol. Aromatase inhibitors were shown to suppress blood and breast cancer tissue estrogen levels in postmenopausal women by 80–95% (Geisler, 2003). However, in both pre- and postmenopausal breast cancer patients estrone sulfatase activity was found to be 50–200 times higher than aromatase activity, with activity of both enzymes greater in post- than in premenopausal women (Pasqualini et al., 1996). Enzyme levels were higher in tumors than in adjacent tissue, which, in turn, were higher than in normal tissue (Chetrite et al., 2000). Tissue levels of estrone, estradiol and their sulfates reflected the enzyme activities. It is considered that formation of estradiol from estrone sulfate is far more important than aromatization in breast tissue (Chetrite et al., 2000; Pasqualini et al., 1996; Santner, Feil, & Santen, 1984).

Several lines of evidence suggest that abnormal regulation of the opposing action of estrogen sulfatases and estrogen sulfotransferases in breast tissue may be responsible for carcinogenesis. Falany and Falany (1996) found that estrogen sulfotransferase was present in human normal mammary epithelial cells, but was absent in ER+ and ER- breast cancer cell lines. Qian, Deng, and Song (1998) showed that the estrogen-responsive human MCF-7 breast cancer cell line lacks estrogen sulfotransferase activity. When this cell line was transfected with estrogen sulfotransferase cDNA, estrogen-stimulated DNA synthesis and cell proliferation was inhibited (Qian et al., 1998). Estrogen sulfotransferase immunoreactivity in human breast carcinoma was significantly associated with a decreased risk of recurrence or improved prognosis. On the other hand, steroid sulfatase immunoreactivity was significantly associated with increased risk of recurrence and worsened prognosis (Suzuki et al., 2003).

Steroid sulfatase inhibitors blocked the ability of estrogen sulfatase to stimulate the growth of carcinogen-induced mammary tumors in ovariecotomized rats (Purohit, Woo, Potter, & Reed, 2000). MCF-7 breast cancer cells over-expressing steroid sulfatase injected into the flanks of ovariecotomized nude mice were used to demonstrate the effect of steroid sulfatase inhibitors in reducing estrogen sulfatase activity and tumorogenicity (Foster et al., 2006). A recent initial trial in postmenopausal women with ER+ metastatic breast cancer demonstrated that a steroid sulfatase inhibitor almost completely blocked steroid sulfatase activity in peripheral blood lymphocytes and tumor tissue (Stanway et al., 2006). A seroepidemiology study by Dorgan et al. (1996) did not detect an association between serum estrone or estrone sulfate levels and the risk of breast cancer. However, the ratio of estrone sulfate to estrone was significantly inversely associated with risk, suggesting that women who develop breast cancer may be less able to metabolize estrone to its inactive form. How estrogen activation and deactivation mechanisms in cells become unbalanced is unknown at present.

7. Breast tissue estrogen content: uptake from the circulation versus synthesis in situ

Levels of estradiol in normal and in malignant breast tissue are similar for pre- and postmenopausal women, despite the large differences in serum levels (Thijssen et al., 1986; van Landeghem et al., 1985). High estradiol levels in postmenopausal breast tissue may result from enhanced uptake from the circulation or from in situ aromatization of androgens and from estrogen sulfate via the sulfatase/17β-HSD pathway. It is estimated that about 75% of estrogens in premenopausal women are synthesized in peripheral tissues and close to 100% after menopause (Labrie, 1991, 2003). However, it is extremely difficult to calculate the relative contributions of uptake from the circulation versus in situ synthesis for an individual organ or tissue, such as the breast.

A number of lines of indirect evidence suggest a role for in situ estrogen synthesis in tumor development that include:

- The presence of the necessary steroidogenic enzymes in breast tissue (Labrie, 2003; Pasqualini, 2004).
- Levels of DHEA, the androgen precursor of estrogens, are many-fold higher in normal and malignant breast tissue for both pre- and postmenopausal women than in their serum (Labrie, 1991; Thijsen et al., 1986).
- ER+ breast tumor tissue contains estradiol (Edery et al., 1981).
- There is little correlation between serum estradiol levels and breast epithelia proliferation (Khan et al., 1999).

Yue, Wang, Hamilton, Demers, and Santen (1998) developed an animal model where aromatase (A-) and sham (A+)-transfected human MCF-7 breast cancer cells were inoculated into ovariecotomized nude mice, which lack peripheral aromatase activity. With the injection of androstenedione and the use of Silastic implants to produce various estradiol levels, it was determined that under physiological conditions, reflecting those in postmenopausal women, in situ aromatization made a major contribution to estradiol levels in breast cancer tissue. Previously, this group showed that rats bearing chemically induced hormone-dependent tumors synthesized about 25% of their estrogen content in situ by the estrogen sulfatase pathway (Masamura, Santner, & Santen, 1986).

A few studies have determined the contribution that local in situ estrogen synthesis made to the estrogen content of normal and malignant breast tissue in postmenopausal women using a double
isotropic technique. Miller et al. (1998) infused 11 patients with $^{14}$C-labeled estrone and $^3$H-labeled androstenedione, 18 h before breast tissue and peripheral blood were taken for analysis. There was considerable variation between breasts with the contribution of in situ synthesis ranging from 0 to 75%. In a subsequent study this group measured the percentage contribution of local estrone synthesis in both normal and tumor tissue from 24 post-menopausal women. Again, there were marked variations between specimens from different patients and the relative proportion of synthesis to uptake was higher in tumors (0–92%, median value 29%) than in normal tissue (0–58%, median value 15%). There was a positive correlation between uptake in normal and malignant tissue (Larinov, Berstein, & Miller, 2002). A small study by Reed et al. (1989) using a similar isotopic infusion technique found that in 3 of 7 subjects there was no or little in situ formation of estrone.

et al. (1989) using a similar isotopic infusion technique found that in 3 of 7 subjects there was no or little in situ formation of estrone. From in vivo experiments, the limit of detection was 0.14 pg mL$^{-1}$. Twelve samples of milk (4 whole, 5 half-skimmed, 3 skimmed) were collected from a French supermarket and analyzed using GC–MS/MS (Courant et al., 2007). The sum of free plus conjugated estradiol ranged from 9.8 to 44.3 pg mL$^{-1}$, with a mean value of 23.0 pg mL$^{-1}$. For estrone the corresponding values were 75.8–277.5 pg mL$^{-1}$ and 152.8 pg mL$^{-1}$, respectively. Eighty percent of estradiol and 96% of estrone were in the conjugated form. Vicini et al. (2008) conducted the most comprehensive survey, with the analysis of 334 samples of retail whole milk collected from 48 states in the USA during a three-week period. RIA, with a sensitivity of 0.8 pg mL$^{-1}$, was used for the assay. The mean value for estradiol was 4.97 ± 0.239 pg mL$^{-1}$. Recently, Farlow et al. (2009) measured estrogen levels in single samples of whole, 2% fat and skim milk in the US using LC-MS/MS (limit of quantitation 0.2 pg mL$^{-1}$). Levels of free estradiol and estrone were 1.0, 1.8, and 2.4 pg mL$^{-1}$ and 10.3, 6.8 and 3.8 pg mL$^{-1}$, respectively. Corresponding values for total estradiol and estrone were 22.1, 22.2, 20.4 pg mL$^{-1}$ and 85.5, 84.6, 65.0 pg mL$^{-1}$, respectively.

8.1. Factors influencing the hormone content of milk

A number of factors can influence the hormone content of milk. Both estradiol and estrone levels increase during the estrous cycle, reaching peak values at estrus, thereafter decreasing to the end of the cycle (Gyawu & Pope, 1990; Monk, Erb, & Mollett, 1975). Hormone levels can also vary with stage of lactation (Gyawu & Pope, 1990). There is considerable inter-individual variation within a herd and values for individual cows fluctuate markedly from week to week (Gyawu & Pope, 1990; Henderson, Karanikolas, Kenealy, & Macmillan, 1994a).

The estrogen level in milk increases during pregnancy. Henderson et al. (1994a) measured the levels of estrone sulfate in milk from four herds. Levels rose progressively during pregnancy from a mean value of 80–100 pg mL$^{-1}$ at 60–80 d of pregnancy to a plateau value of around 1000 pg mL$^{-1}$ at 181–200 d. For non-pregnant cows in the herds, estrone sulfate concentration ranged from non-detected to 110 pg mL$^{-1}$ with a mean value of 59 pg mL$^{-1}$ Malekinejad et al. (2006) reported that the level of free estrone in raw milk from non-pregnant cows and cows in the first, second and third trimester of gestation was 6.2, 9.2, 57 and 118 pg mL$^{-1}$, respectively. Corresponding values for free estradiol were 5.6, 10.2, 20.4 and 21.3 pg mL$^{-1}$, respectively. For total estrogens (free + conjugated and for different cows from the above), estrone levels in the first, second and third trimester milk were 7.9, 452 and 1266 pg mL$^{-1}$, and for estradiol 18.6, 51.4 and 51.2 pg mL$^{-1}$, respectively.

Pape-Zambito et al. (2007) found that mean free estradiol levels of milk from non-pregnant cows, early pregnant cows (1–140 d) and mid-pregnant cows (141–210 d) were 1.3, 0.9 and 3.0 pg mL$^{-1}$, respectively. In a further study (Pape-Zambito, Magliaro, & Kensinger, 2008) a group of cows was followed throughout pregnancy. Milk free estrone concentrations averaged 0.6, 7.9 and 27.1 pg mL$^{-1}$ during the first, second and third trimester, respectively. Corresponding values for estradiol were 0.3, 0.9 and 5.0 pg mL$^{-1}$, respectively.

Free estrogens are lipophilic and Pape-Zambito et al. (2008) and Pape-Zambito, Roberts, and Kensinger (2010) found both estrone and estradiol levels were significantly correlated with the fat content of whole milk. Malekinejad et al. (2006) found that for 0%, 1.5% and 3.5% fat milk the free estrone content was 8.2, 17.1 and 25 pg mL$^{-1}$, respectively.
20.0 pg mL\(^{-1}\), respectively. Corresponding values for estradiol were 10.3, 13.9 and 20.6 pg mL\(^{-1}\), respectively. On the other hand, another study found no relationship between total estrogen content and the fat content of milk (Courant et al., 2007). This is undoubtedly due to the fact that conjugated estrogens, by far the major component of milk estrogens, are more soluble in aqueous solution. Pasteurization and homogenization of raw milk do not appear to affect the estrogen content (Pape-Zambito et al., 2010). Ganmaa and Sato (2005), Ganmaa, Wang, Qin, Hoshi, and Sato (2001), Maruyama, Oshima, and Ohyama (2010), Qin et al. (2004) and others have suggested that compared with milk produced 100 years ago, modern herd bulk milk contains a larger proportion of milk from cows in the latter half of pregnancy, and thus has elevated levels of estrogens, which may contribute to reproductive disorders and cancer at hormone-responsive sites. However, as noted above, the increased estrogen levels during late pregnancy is mostly due to estrone sulfate, which is largely biologically inactive. In addition, during the past 60–70 years milk production per cow has increased about 5-fold due to improved genetics for milk production coupled with changes in nutritional management (Capper, Cady, & Bauman, 2009). Estradiol concentrations are negatively correlated with milk yield (Pape-Zambito et al., 2008). This effect is probably due to the fact that high milk intake increases liver blood flow and metabolic clearance rate of estradiol by the liver (Sangsritavong, Combs, Sartori, Armentano, & Wiltbank, 2002).

Pape-Zambito et al. (2008) estimate that the majority of cows producing milk for consumption would have less than 2 pg mL\(^{-1}\) of estradiol. This estimate is based on their studies with herd milk and milk from pregnant cows and because early lactation cows have high milk yields and farmers generally dry off cows at 60 days before the next expected calving. Thus, there is no evidence that the levels of estrogen in modern commercial milk are higher than 100 years ago.

9. Absorption and metabolism of estrogens from milk and its products

Estradiol in consumed dairy products is absorbed from the intestine. The intestinal mucosa contains enzymes capable of the transformation of estradiol to estrone and the formation of estrogen sulfate and glucuronide conjugates. These metabolites and any free estradiol pass to the portal circulation and rapidly pass to the liver where near-complete metabolism to estrone, estrone sulfate (the major conjugate) and some estrogen glucuronides and hydroxylated conjugates occurs (Lobo & Cassidy, 1992; Longcope et al., 1985). Part of the conjugated estrogens pass to the kidneys and are excreted in urine. Most of the remainder is excreted with bile to the intestinal lumen. Here, some of the conjugated estrogens may be deconjugated by bacterial β-glucuronidases, but most of these are re-conjugated by intestinal steroid sulfotransferases and glucuronosyltransferases and along with the majority of the remaining bile-derived estrogen conjugates are re-absorbed and pass to the liver (enterohepatic circulation). A portion escapes this enterohepatic circulation and is excreted in the faeces. Any free estradiol will be conjugated at the next pass of the liver (Adlercreutz & Martin, 1980; Adlercreutz, Martin, Jarvenpaa, & Fotis, 1979). Overall, it is estimated that as a result of metabolism by the intestinal mucosa and first pass to the liver, the bioavailability of oral estradiol is only in the range of 2–5% (Dusterberg, Schmidt-Gollwitzer, & Hummel, 1985; Kuhnz, Gansau, & Mahler, 1993).

As part of a German market basket survey, Hartmann et al. (1998) determined the natural occurrence of steroid hormones in food. Based on previously published national nutritional data they estimated the daily intake of estrogens (estrone plus estradiol) from milk products was 0.06 μg for men and 0.05 μg for women. These values were due largely to the relatively bio-inactive estrone and both estrone and estradiol were predominantly present as inactive conjugates. Based on recent studies with sensitive assays (Farlow et al., 2009; Malekiunejad et al., 2006; Pape-Zambito et al., 2007, 2008, 2010; Vicini et al., 2008), it appears unlikely that free estradiol levels in commercial milk would exceed 5.0 pg mL\(^{-1}\). Thus, consumption of 1.5 L of milk or equivalent dairy products per day would result in a daily estradiol intake of not more than 7.5 ng, of which no more than about 0.38 ng would survive first pass metabolism to the liver. This value must be considered in the context of daily excretion rates for estradiol in humans. In premenopausal women the daily production of estradiol varies between 0.08 and 1.00 mg, depending upon the phase of the menstrual cycle (Hsueh & Billig, 1995). With the cessation of ovarian function after menopause, daily estradiol production decreases to around 12 μg, which is mainly derived from estrone, now the predominant estrogen and produced in peripheral tissues through aromatization by the action of the aromatase enzyme (Goldfin & Monroe, 1986). Production rates for estrone range from 40 μg d\(^{-1}\) for slender women to 200 μg d\(^{-1}\) for obese women (O'Dell, 1995). In men estradiol production is about 45 μg d\(^{-1}\) (Kauffman & Vermeulen, 2005). Estradiol production in prepubertal children has not been determined directly, but it is considered values will be low (Andersson & Skakkebæk, 1999). Thus, in the case of premenopausal women, intake of around 7.5 ng d\(^{-1}\) of estradiol from 1.5 L of milk or equivalent would represent merely 0.00076–0.0094% of their daily production and only 5% of this intake would survive the first pass of the liver in a bioactive form. The percentages for postmenopausal women, prepubertal children and men would be higher.

The Joint FAO/WHO Expert Committee on Food Additives (WHO, 2000) established an acceptable daily intake for estradiol of 0–50 ng kg\(^{-1}\) of body weight. This figure was based on changes in several hormone-dependent parameters in postmenopausal women. A safety factor of 10 was used to account for normal variation among individuals, and an additional factor of 10 was added to protect sensitive individuals. Accordingly, estradiol consumption from dairy products should account for only around 0.25% of the FAO/WHO upper acceptable daily intake value.

Milk contains estrone of which around 90% is estrone sulfate (Henderson, Cambieris, Simmons, Stars, & Hardie, 1994b). Estrone has low biological activity and estrone sulfate is inactive. It is possible that some of the small quantity of estrone sulfate in milk that survives metabolism during first pass to the liver may be converted to estrone by sulfatases then to estradiol by 17β-HSD. However, milk-derived estrogens are but a small fraction of a large circulating pool. For instance, for postmenopausal women in the Nurse’s Health study (Hankinson et al., 1995) mean concentrations of estrone and estrone sulfate were 18- and 98-fold higher than bioavailable estradiol. In addition, there are vastly higher levels of circulating DHEA-S (Labrie, 2003), and even higher levels in breast tissue (Thijssen et al., 1986), which can be bioconverted to estrone and estradiol if required by the cell. Overall, estrogen-sensitive cells possess multiple mechanisms to obtain estradiol for their growth and maintenance and to inactivate surplus to requirements. Coupled with the relatively minute amount of dairy product-derived estradiol surviving intestinal absorption and first pass liver metabolism, this makes it unlikely that estradiol from this source would influence cancer development.

10. Physiological influence of various exogenous sources of estrogen

The estrogen content of milk, its contribution to the body’s estrogen pool and its physiological significance may be viewed in
relation to the influence of a number of external factors on serum estrogen levels. Many factors have been studied but BMI appears to be the most important determinant. Data from the Nurses’ Health Study (Hankinson et al., 1995) showed that in postmenopausal women serum estrogen levels were positively associated with BMI. Mean serum estradiol levels ranged from 4.7 pg mL$^{-1}$ in the lowest quintile of BMI ($<21$ kg m$^{-2}$) to 10.0 pg mL$^{-1}$ in the highest quintile ($>29$ kg m$^{-2}$). For bioavailable estradiol, the corresponding values were 0.8 and 3.3 pg mL$^{-1}$. A pooled re-analysis of individual data from 8 prospective studies showed similar variations (Endogenous Hormones and Breast Cancer Collaborative Group, 2003).

Dietary components may influence intestinal function and the bacterial population. Changes in the number of $\beta$-glucuronidase-producing bacteria can influence deconjugation of estrogens, affect the enterohepatic circulation and the level of estrogens excreted in faeces and urine and their level in blood (Goldin & Gorbach, 1994). Many studies investigated the role of dietary components such as fat, protein and fiber, on serum estrogen levels, but most suffered from methodological faults, small sample size and lacked controls. The Nurses’ Health Study found associations between different dietary patterns and serum estrogen levels in postmenopausal women, but the associations were lost after adjusting for BMI (Fung, T. H., Barbara Willett, & Hankinson, 2007). The effect of animal products and their nutrient components on circulating estrogens levels in postmenopausal women was investigated in the large Melbourne Collaborative Study (Brinkman et al., 2010). None of the food items or nutrients explained more than 1% of the total variation in concentration of any steroid hormone.

For clinical intervention studies, Carruba et al. (2006) randomized postmenopausal women to receive their normal diet or a traditional Mediterranean diet (intervention). After 6 months, the urinary total estrogen concentration in the intervention group decreased by 40%. This decrease was largely driven by the estrogen metabolites 2-hydroxy- and 16-ketoestradiol and 17-epiestriol. Estradiol represented only 1.16% of total estrogens and this level was significantly higher than the baseline value. However, during the study, subjects in the intervention group consumed significantly less calories than at baseline. The intervention group of postmenopausal women in the large Women’s Health Initiative randomized controlled dietary modification trial consumed a low-fat diet with increased intake of fruit, vegetables and grains compared to their normal diet. Serum estrogen levels were measured in a sub-group of women at baseline and after 1 year of intervention. Estradiol concentrations decreased from 7.6 to 6.7 pg mL$^{-1}$. However, during this period there was a decrease of 2.4 kg in the weight of women in the intervention group (Prentice et al., 2006). A change in diet to one low in animal fat and refined carbohydrates and rich in low-glycemic-index foods, monounsaturated and n-3 polyunsaturated fatty acids and phytoestrogens in a small group of postmenopausal women resulted in a fall in serum estradiol levels from 8.62 to 7.07 pg mL$^{-1}$ after 4.5 months intervention. During this time, their BMI decreased from 26.88 to 25.26 kg m$^{-2}$ (Berrino et al., 2001).

Based on the limited data available, different dietary patterns may be responsible for a 10–20% change in serum estradiol in postmenopausal women, but about one-half of this effect may be due to weight change. Similar changes in serum estradiol levels as a result of dietary modification in premenopausal women may also apply (Goldin et al., 1981).

The effect of oral contraceptive use and hormone replacement therapy (HRT) on serum and tissue estradiol concentrations is also informative and illustrates one of the paradoxes associated with the role of estradiol in cancer development. A sub-group of postmenopausal women in the Women’s Health Initiative randomized controlled clinical trial of estrogen therapy that received 0.625 mg d$^{-1}$ of conjugated equine estrogens (CEE) had serum estrogen levels measured at baseline and after 1 year of therapy (Edslesen et al., 2010). Estradiol levels increased from 13.3 to 35.5 pg mL$^{-1}$, bioavailable estradiol from 8.9 to 16.1 pg mL$^{-1}$ and free estradiol from 0.4 to 0.6 pg mL$^{-1}$. Estrone levels increased from 41.4 to 149.9 pg mL$^{-1}$. After a mean of 10.7 years of follow-up in the intervention phase of the Women’s Health Initiative randomized controlled trial (LaCroix et al., 2011), the hazard ratio for breast cancer in postmenopausal women who used 0.625 mg d$^{-1}$ of CEE for a median of 5.9 years compared to non-users was 0.77 (0.62–0.95) Three other small randomized controlled trials of estrogen-only therapy reviewed by Collins, Blake, and Crosignani (2005), found no excess risk compared with placebo. Epidemiological evidence from the large Nurses’ Health Study suggested that women who had undergone a hysterectomy and used estrogen-only therapy for less than 20 years did not have an increased risk of developing breast cancer. However, longer duration of usage was associated with higher risk, primarily for ER$^+$ and progesterone receptor positive breast cancers (Chen et al., 2006).

Use of oral contraceptives by premenopausal women causes a suppression of ovarian function. As a result the elevated levels of estradiol during mid-cycle and again during the mid-luteal phase are suppressed several fold to levels at or below levels found in the first half of the follicular phase in non-users. A similar suppression occurs for estrone (Carr & Bradshaw, 1998; Gaspard, Dubois, Gillian, Franchimont, & Duviver, 1984). In addition, in breast tissue, oral contraceptive use suppressed estradiol levels 7.8-fold and estrone levels 2.9-fold compared to non-users (O’Brien, Anandijwala, & Price, 1997). However, epidemiological evidence for women using oral contraceptives and were subjected to these large reductions in serum and tissue estrogens does not show a reduced risk for subsequent breast cancer (Hunter et al., 2010; Kahlenborn, Modugno, Potter, & Severs, 2006).

Around 30 years ago, several observation studies suggested that hormonal changes in women might be associated with the risk of colon cancer. However, the results of these studies were not consistent. During the period 1961–1990 the sex-specific rates for colon cancer incidence in men increased by 16%, whereas in women the incidence declined by 21% (Potter, 1995). This inequality was considered to be due to hormone differences. HRT use was considered a possible determinant of the beneficial effect in women, and a number of epidemiological studies investigated this relationship. Hebert-Croteau (1998) conducted a meta-analysis of 11 case-control studies, 7 cohort studies and a randomized controlled trial. A summary RR of 0.85 (0.73–0.99) was found between ever versus never users of HRT and the risk of colon cancer. The estimated RR was lower among current and recent users, RR 0.69 (0.52–0.91) as compared to short-term users, RR 0.88 (0.64–1.21). This meta-analysis did not include the 14-year follow-up data from the large Nurses’ Health Study (Grodstein et al., 1998), which showed current use of postmenopausal HRT was associated with a RR of 0.65 (0.50–0.83). This association was attenuated to a RR of 0.84 (0.67–1.05) in past users of HRT. A subsequent meta-analysis that included the up-dated data from the Nurses’ Health Study (Grodstein, Newcomb, & Stamper, 1999) found that women who had ever taken postmenopausal HRT, compared to never users had a RR of 0.80 (0.74–0.86) for colon cancer and a RR of 0.81 (0.72–0.92) for rectal cancer. Much of the reduction in colorectal cancer was limited to current HRT users (RR, 0.86, 0.59–0.74).

In the Women’s Health Initiative Randomized Controlled Trial (Rossouw et al., 2002), the HR for participants who received 0.625 mg d$^{-1}$ CEE plus 2.5 mg d$^{-1}$ medroxyprogesterone acetae compared with placebo was 0.63 (0.43–0.92). On the other hand, in the CEE-only arm (LaCroix et al., 2011), the HR for CEE compared
with placebo was 1.15 (0.081–1.64). However, the number of colon cancer cases during the trial was small. A large case-control study by Hoffmeister, Raum, Krtschil, Chang-Claude, and Brenner (2009) found the risk of colorectal cancer decreased in both estrogen-only therapy, RR 0.42 (0.23–0.78) and in combination therapy, RR 0.60 (0.41–0.87).

The benefit of estradiol for colorectal carcinogenesis was confirmed in animal studies. For instance, Smirnoff, Lie, Gnaisnky, Shany, and Schwartz (1999) demonstrated that tumor numbers in ovariectomized mice induced by dimethylhydrazine, were reduced by 72% when treated with estradiol. Reduced cell growth and increased apoptotic activity, in a dose-dependent manner, was noted in young adult mouse colonocytes when treated with physiological levels of estradiol. In addition, ovariectomy in ovariectomized mice exhibited a significant protection against preneoplastic lesions (Weige, Allred, & Allred, 2009).

11. Epidemiological evidence

Because it is not possible to conduct appropriate clinical trials to prove unequivocally that the small quantity of estrogens in dairy products do not influence cancer development, by default, epidemiological studies, despite their limitations, may provide evidence on the safety of dairy product consumption.

11.1. Breast cancer

Missner, Smith-Warner, and Spiegelman (2002) conducted a pooled analysis of 8 cohort studies that provided 351,041 subjects, 7379 of whom were diagnosed with breast cancer. No significant association was found between dairy product consumption and breast cancer risk. A review of 10 cohort and 36 case-control studies by Moorman and Terry (2004) concluded that the epidemiological evidence did not support a strong association between consumption of milk or other dairy products and the risk of breast cancer. In later prospective studies McCullough et al. (2005), from the Cancer Prevention Study II, reported that dairy product consumption was inversely associated with postmenopausal breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (Pala et al., 2009), which recruited cohorts from 10 European countries, did not find dairy product consumption a risk factor for breast cancer.

Exposure to initiating events during childhood, adolescence and early adulthood, when the mammary gland is attaining adult stage morphology, may influence the risk of breast cancer later in life. A review of 4 case-control and 3 cohort studies (Parodi, 2005) did not find an association between adolescent dietary product consumption and subsequent breast cancer development. A later large study of participants from the Nurses’ Health Study and the Nurses’ Health Study II found that consumption of whole milk as part of a preschool diet was associated with a slightly decreased risk of adult breast cancer (Michels, Rosner, Chumlea, Colditz, & Willett, 2006). Examination of adolescence diet in the Nurses’ Health Study II found no overall association for total milk or total dairy intake and risk of breast cancer; however, a nonsignificant inverse trend between breast cancer and low-fat milk and low-fat dairy was noted (Linos, Willett, Cho, & Frazier, 2010). Sixty-five year follow-up of the Boyd Orr cohort showed that a family diet rich in dairy products during childhood was not associated with adult breast cancer risk (van der Pols et al., 2007). Epidemiology suggests that dairy product consumption during various stages of the life cycle is safe and not associated with a risk of breast cancer. However, because dairy products contain calcium together with a range of lipid anticancer agents (Parodi, 2005), such analyses cannot unequivocally exonerate estrogens in milk and its products as possible carcinogens.

11.2. Ovarian cancer

Genkinger et al. (2006) conducted a pooled analysis of 12 cohort studies representing 553,217 women among whom 2132 epithelial ovarian cancer cases were identified. No associations were observed between intake of specific dairy foods and ovarian cancer risk. Subsequently, it was also found that there were no associations between intakes of various dairy foods and the risk of ovarian cancer among participants in the Netherlands Cohort Study on Diet and Cancer (Mommers, Schouten, Goldbohm, & van den Brandt, 2006). Higher intakes of total dairy foods were associated with a statistically significant decreased risk of ovarian cancer in the Breast Cancer Detection Demonstration Project cohort (Koralek et al., 2006).

11.3. Endometrial cancer

The role of dairy products in endometrial cancer has not been studied widely. A systematic literature review and meta-analysis of the available evidence by Bandera, Kushi, Moore, Gifkins, and McCullough (2007) found no support for an association between dairy product consumption and risk of endometrial cancer.

11.4. Prostate cancer

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 2007 report on Food, Nutrition, Physical Activity and the Prevention of Cancer (The World Cancer Research Fund/American Institute for Cancer Research, 2007) considered that there was limited evidence suggesting that high consumption of milk and dairy products is a cause of prostate cancer. The WCRF/AICR Panel suggested that high calcium intake from dairy products down-regulates the formation of 1,25-dihydroxyvitamin D$_3$ from Vitamin D, thereby increasing cell proliferation in the prostate. Also, consumption of milk products increases blood levels of insulin-like growth factor-1, which has been associated with increased prostate cancer risk in some studies. The Panel did not implicate estrogens in prostate cancer risk.

Since the WCRF/AICR report, numerous prospective studies have presented results that included sub-group analyses of associations between types of milk and dairy products and stage of prostate cancer. There were often contradictory results, but overall the more recent studies do not provide strong support for an increased risk of prostate cancer with dairy product consumption (Parodi, 2009).

11.5. Colon cancer

Numerous epidemiological studies have demonstrated a negative association between dairy product consumption, particularly milk, and the risk of colorectal cancer. Huncharek, Muscat, and Kupelnick (2009) conducted a meta-analysis of 26,335 cases from 60 observational studies. The summary RR for high milk and dairy product intake, respectively, on colon cancer risk and thus in studies where colorectal cancer was the end point; summary RR was attenuated to 0.90 (0.81–1.00). Calcium in milk is believed to be the principal agent responsible for its protective action (Holt, 2008; Pufulete, 2008), although lipid components like conjugated linoleic acid, butyric acid and sphingomyelin (Larsson, Bergkvist, & Wolk, 2005; Parodi, 1997) and milk proteins, especially whey proteins (Parodi, 2007) may also
contribute. Whether the small amount of bioactive estradiol in milk has any impact on colon carcinogenesis is unknown, but epidemiology suggests it causes no harm.

12. Conclusions

Although several lines of evidence suggest a role for estrogens in cancer at hormone-responsive sites, such as the breast, ovaries, endometrium and the prostate, the mechanisms remain elusive. This may result from estrogens acting in concert with other hormones, growth factors and cytokines and presents a major research problem. Many studies have determined associations between serum estrogen levels and the risk of cancer at estrogen-responsive sites. The association is robust for postmenopausal breast cancer, but less so for premenopausal women, strong for endometrial cancer and null for ovarian and prostate cancer. However, there is no correlation between circulating levels of estrogens and their precursors with their levels in tissues. It is now recognized that the hormone-responsive tissues contain all the necessary steroidogenic enzymes for the synthesis of estrogens from androgen precursors. In addition, the tissues contain enzymes responsible for conjugation of bioactive estrogens to inactive conjugates in order to maintain estradiol homeostasis. A few studies have measured the contributions of estrogens from in situ synthesis and uptake from the circulation in normal and malignant breast tissue. Results show a large inter-individual variation for in situ synthesis with values ranging from 0 to over 90%, overall values were higher in cancer tissue. Reasons for, and the significance of, the large variation in source of tissue estrogens, in conjunction with the studies of a level of the activities of metabolizing enzymes require further investigation.

Cows’ milk contains estrogens. Recent high sensitivity assays suggest that commercial milk would not contain more than 5 pg mL of free estradiol. On ingestion only 2–5% of this bioactive form survives metabolism in the intestinal mucosa and first pass to the liver. This amount is only a minute fraction of daily production levels in women and men and is far less than possible fluctuations in serum levels due to diet, weight excess and use of hormone therapy. Expected daily estradiol intake from dairy products represents only about 0.25% of the FAO/WHO upper acceptable daily intake of exogenous estradiol. Given the multiple mechanisms cells possess to obtain estradiol for their function, it is most unlikely that the small amount of exogenous estradiol provided by dairy products would influence carcinogenesis at estrogen-responsive sites. Epidemiological studies do not show an association between dairy product consumption and risk of cancer of the breast, ovaries and endometrium. There is a slight positive association with prostate cancer, but estrogens have not been implicated as an etiologic factor.

References


References


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