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Energy balance and cancer: the role of sex hormones

Timothy J. Key*, Naomi E. Allen, Pia K. Verkasalo and Emily Banks
Imperial Cancer Research Fund, Cancer Epidemiology Unit, University of Oxford, Oxford OX2 6HE, UK

Energy balance can affect the risk for hormone-related cancers by altering sex hormone levels. Energy intake and expenditure are difficult to measure in epidemiological studies, but a chronic excess of intake relative to expenditure leads to a high BMI, which can be accurately measured. In premenopausal women obesity has little effect on the serum concentration of oestradiol, but causes an increase in the frequency of anovular menstrual cycles and thus a reduction in progesterone levels; these changes lead to a large increase in the risk for endometrial cancer, but little change, or a small decrease, in the risk for breast cancer. In post-menopausal women oestradiol levels are not regulated by negative feedback, and obesity causes an increase in the serum concentration of bioavailable oestradiol; this factor causes increases in the risk for both endometrial cancer and breast cancer. The development of ovarian cancer appears to be related more strongly to the frequency of ovulation than to direct effects of circulating levels of sex hormones, and BMI is not clearly associated with the risk for ovarian cancer. In men, increasing BMI has little effect on bioavailable androgen levels, and any effect of obesity on prostate cancer risk is small.

Energy balance: Obesity: Cancer: Sex hormones

Energy balance and cancer risk

The potential importance of energy balance as a determinant of cancer risk was suggested by animal experiments conducted in the first half of the 20th century, which showed that energy restriction in an otherwise adequate diet can reduce the development of various tumours and slow the growth of existing tumours in rats and mice (McCay *et al*. 1935; Tannenbaum, 1940). Numerous subsequent studies, particularly of mammary cancer in rodents, have established beyond question that a low energy intake can reduce tumour incidence (Pariza, 1987; Freedman *et al*. 1990). The most important question raised by these experiments is whether such an effect may also operate in human subjects within the range of energy intakes encountered in human populations and compatible with normal healthy life. The possible effects of energy balance on cancer rates in human subjects can be considered in relation to energy balance during growth and energy balance in adult life.

There are few data relating energy intake during childhood and subsequent cancer rates. In a small retrospective cohort study Frankel *et al*. (1998) linked records of dietary intake during childhood with subsequent cancer mortality. They observed a small increase in mortality from cancers not related to smoking in association with a relatively high estimated energy intake at ages ≤ 16 years; leg length in childhood, which may be particularly sensitive to energy intake, was also positively associated with mortality from cancers not related to smoking in this cohort (Gunnell *et al*. 1998).

A number of epidemiological studies have investigated the association between adult height and cancer. Height is determined by genetic and nutritional factors, and a relatively short height may be a marker for a restricted food intake during growth. In general, positive associations have been observed between height and risk for cancers not related to smoking, including breast cancer (Micozzi, 1985) and prostate cancer (Hebert *et al*. 1998). The mechanism for this association is not known, but it could be related to the number of susceptible cells in the target tissues (Albanes & Winick, 1988; Albanes, 1998).

The purpose of the present paper is to review the effects of energy intake on cancer risk which may be mediated by

Abbreviation: SHBG, sex hormone-binding globulin.
***Corresponding author:** Dr Timothy J. Key, fax +44 1865 310 545, email key@icrf.icnet.uk

altering the levels of endogenous sex hormones (principally oestradiol in women and testosterone in men). Four major cancers which are generally regarded as hormone-related are discussed: endometrium, breast and ovary in women, and prostate in men. The relationships of sex hormones with the development of cancer of the testis are poorly understood and are not discussed here. Other recent detailed reviews of energy balance and cancer risk include Albanes (1990), Thorling (1996) and Gerber & Corpet (1999).

Sex hormones and cancer

Sex hormones are important, either directly or indirectly, in the aetiology of cancers of the endometrium, breast, ovary and prostate. The growth and development of these organs is controlled by sex hormones, and epidemiological studies have shown that the risk for developing these cancers is associated with various hormone-related factors such as age at menarche, pregnancy and age at menopause. There is also direct evidence that the risk for some of these cancers is related to the circulating serum concentration of various sex hormones.

The mechanism by which sex hormones affect cancer risk is probably largely through determining the number and mitotic rate of the epithelial cells in the organ concerned (Albanes & Winick, 1988; Cohen & Ellwein, 1990). High mitotic rates can increase cancer risk by increasing the chance of mutations occurring and of being replicated before they are repaired, and can also increase the growth of early tumours (Cohen & Ellwein, 1990; Preston-Martin *et al*. 1990). In the case of oestrogens, it has also been argued that certain metabolites of oestradiol may cause mutations by directly damaging the DNA (Liehr, 2000), but the importance of this possible mechanism has not been established, and we think that the major role of sex hormones in cancer is likely to be as determinants of cell number and mitotic rate.

Sex hormones and BMI

Age at menarche in women and age at puberty in men

Sex hormone levels are low during childhood in both girls and boys, and increase markedly during puberty. In women the age at first menstrual period (menarche) is well defined and has been extensively studied. In men the age of puberty is more difficult to define and fewer data are available. However, it is clear that one factor which can delay the age at menarche is a restricted food intake, and it is likely that this factor may also delay the age of puberty in men. A restricted food intake and/or a high level of physical activity during growth will result in a restricted positive energy balance, which causes a low BMI and a delay in the age at menarche (Meyer *et al*. 1990; Petridou *et al*. 1996). Sexual maturation may also be delayed by non-nutritional factors such as recurrent infections.

Homeostatic control of hormone levels

In premenopausal women and in men serum concentrations of oestrogens and androgens respectively are homeostatically controlled through feedback loops involving the hypothalamus and the anterior pituitary. In contrast, among post-menopausal women oestrogens are largely produced by conversion in the adipose tissue and other peripheral tissues from precursor androgens (largely androstenedione) secreted by the adrenal glands; as far as is known, this oestrogen synthesis in post-menopausal women is not controlled by any feedback mechanism and is essentially unregulated. This physiological difference between premenopausal women and men, on the one hand, and post-menopausal women, on the other hand, has profound consequences for the relationships between BMI and circulating sex hormone levels.

The role of sex hormone-binding globulin

Sex hormone-binding globulin (SHBG) is a glycoprotein, synthesised in the liver, which has specific binding sites for oestrogens and androgens. Most of the oestradiol and testosterone in the blood is bound either tightly to SHBG (40–50 %) or more loosely to albumin (also about 40–50 %), with only about 2 % non-protein-bound or free. In general, only the free fraction (or perhaps the non-SHBG-bound fraction, which is very strongly correlated with the free fraction) is available to enter the cells and thus bind with steroid receptors. Since the binding capacity of albumin is very high, the primary determinant of the proportion of the steroid which is free is the concentration of SHBG; an increase in serum SHBG concentration produces a corresponding reduction in the proportion of free steroid (Dunn *et al*. 1981). The effect is greater for testosterone than for oestradiol, in that a given change in SHBG causes a larger change in the proportion of testosterone which is free than in the proportion of oestradiol which is free.

The interrelationships between oestrogens, androgens and SHBG are complex. SHBG regulates the proportions of the sex steroids which are bound and free, but the sex steroids themselves can also affect the concentration of SHBG. On average, men have lower serum concentrations of SHBG than women, and the concentration of SHBG can rise in response to oestrogens and fall in response to androgens. However, these effects of steroids on SHBG are in most circumstances less obvious than the effects of SHBG on the sex steroids. Factors which alter SHBG (such as BMI, described later) can cause changes in the total serum concentration of sex steroids because the control of sex hormone production by negative feedback is regulated by the concentration of free steroid; if SHBG falls, the proportion of free steroid increases and therefore steroid production is reduced in order to maintain a constant concentration of free steroid.

Numerous studies have shown without exception that the serum concentration of SHBG falls with increasing BMI. This relationship is seen equally in premenopausal women, in post-menopausal women and in men. The average concentration of SHBG is about twice as high in thin individuals (BMI $< 20\,kg/m^2$) than in obese individuals (BMI $> 30\,kg/m^2$). The mechanism for this effect has not been completely established, but may be largely due to the rise in insulin levels with increasing BMI (Franks *et al*. 1991).

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Oestrogens in premenopausal women

In premenopausal women, the primary source of oestradiol is production by the ovaries; it is also produced from the aromatization of adrenal androgens in the adipose tissue, as in post-menopausal women, but this production is quantitatively minor compared with ovarian production. The production of oestradiol by the ovaries is regulated by the hypothalamus and anterior pituitary in a rather complex manner during the menstrual cycle, with phases of both negative and positive feedback, but the overall effect of these mechanisms is to regulate serum oestradiol concentrations.

As BMI increases, SHBG in premenopausal women falls and there may be a small fall in total oestradiol, but the concentration of free oestradiol remains approximately constant (Fig. 1), implying that the homeostatic control of free oestradiol is effective, and that within the BMI range of 20–30 kg/m^2 there is little variation in biologically-available oestradiol. With clinical obesity (BMI > 30 kg/m^2), there is an increased incidence of anovulatory menstrual cycles. The effect of this factor on average serum concentrations of oestradiol is unclear; oestradiol concentrations during the early follicular phase of the menstrual cycle may be higher than those in thin women because of extra-ovarian production, but oestradiol concentrations during the second half of the menstrual cycle may be lower than those in thin ovulatory women because of the failure of ovulation and therefore the lack of oestradiol production by a functional corpus luteum. The average levels of oestradiol in obese women appear to be similar to or a little lower than those in normal-weight women (Zhang *et al*. 1984; Grenman *et al*. 1986).

The ovaries of premenopausal women also produce progesterone, which plays a key role in the aetiology of endometrial cancer and may be important in the aetiology of breast cancer. Alterations in BMI within the range of 20–30 kg/m^2 have not been shown to have major effects on progesterone levels, but with clinical obesity the incidence of anovulatory cycles increases markedly and these cycles have low levels of progesterone due to the failure to produce a corpus luteum (Sherman & Korenman, 1974).

Oestrogens in post-menopausal women

In post-menopausal women the ovaries do not produce oestradiol or progesterone. Serum oestradiol concentrations fall to about 10 % of those observed in premenopausal women, and progesterone concentrations fall to extremely low levels. The principal source of oestradiol in post-menopausal women is from the androgen androstenedione which is secreted by the adrenal glands and is aromatized by the enzyme aromatase to oestrone in the peripheral tissue, mainly the adipose tissue; some of the oestrone is then converted to oestradiol (Siiteri & MacDonald, 1973; Judd *et al*. 1982).

This production of oestradiol in post-menopausal women is not regulated by feedback. Thus, obese post-menopausal women have much higher serum oestradiol concentrations than thin post-menopausal women (up to about 2-fold higher). Since SHBG falls with increasing BMI, the proportion of free oestradiol increases, and therefore the increase in the concentration of free oestradiol with increasing BMI is even greater than the increase in the concentration of total oestradiol (greater than 2-fold; Fig. 1).

Androgens in men

Testosterone production is regulated by negative feedback of circulating free testosterone on luteinising hormone secretion. An increase in BMI is associated with large reductions in both SHBG and total testosterone, but with little or no change in free testosterone, at least within the BMI range of 20–30 kg/m^2 (Fig. 1; also, see Field *et al*. 1994; Wu *et al*. 1995; Vermeulen *et al*. 1996). The mechanisms underlying these hormonal changes are not fully understood, but may be associated with the metabolic and hormonal imbalance known as insulin-resistance syndrome, leading to higher circulating insulin levels. This change results in a reduction in SHBG production (Pasquali *et al*. 1995), which causes an increase in the proportion of free testosterone and a corresponding fall in testosterone production via the negative feedback mechanism to maintain the concentration of free testosterone at a constant level. In severely obese men (BMI > 40 kg/m^2), low luteinising hormone and free testosterone concentrations have been reported, indicating impaired effectiveness of the feedback regulation of free testosterone levels (Vermeulen *et al*. 1993).

Endometrial cancer

Reproductive factors and sex hormones

The risk for endometrial cancer is largely determined by the exposure of the endometrium to oestrogens in the absence of progestagens (Key & Pike, 1988*a*). No data are available from prospective studies of endogenous sex hormones and endometrial cancer risk, but data from case–control studies in post-menopausal women have shown that high oestrogen levels are associated with an increase in risk (Potischman *et al*. 1996). The use of hormone-replacement therapy containing oestrogen alone also causes a large increase in risk, whereas use of hormone-replacement therapy containing a progestagen as well as an oestrogen causes a smaller increase in risk, which may be completely eliminated if the progestagen is used continuously (Beresford *et al*. 1997; Pike *et al*. 1997; Weiderpass *et al*. 1999).

BMI

Obesity is a major risk factor for endometrial cancer. In premenopausal women the risk increases moderately in overweight women, and may reach very high risks (up to 20-fold) in women with a BMI ≥ 30 kg/m^2 compared with women with a BMI < 20 kg/m^2 (Henderson *et al*. 1983; La Vecchia *et al*. 1984). In post-menopausal women risk increases about 3-fold in overweight women (Folsom *et al*. 1989) and may reach about 5- to 10-fold higher in obese women (BMI > 30 kg/m^2) compared with thin women (BMI < 20 kg/m^2; La Vecchia *et al*. 1984; Weiderpass *et al*. 2000).

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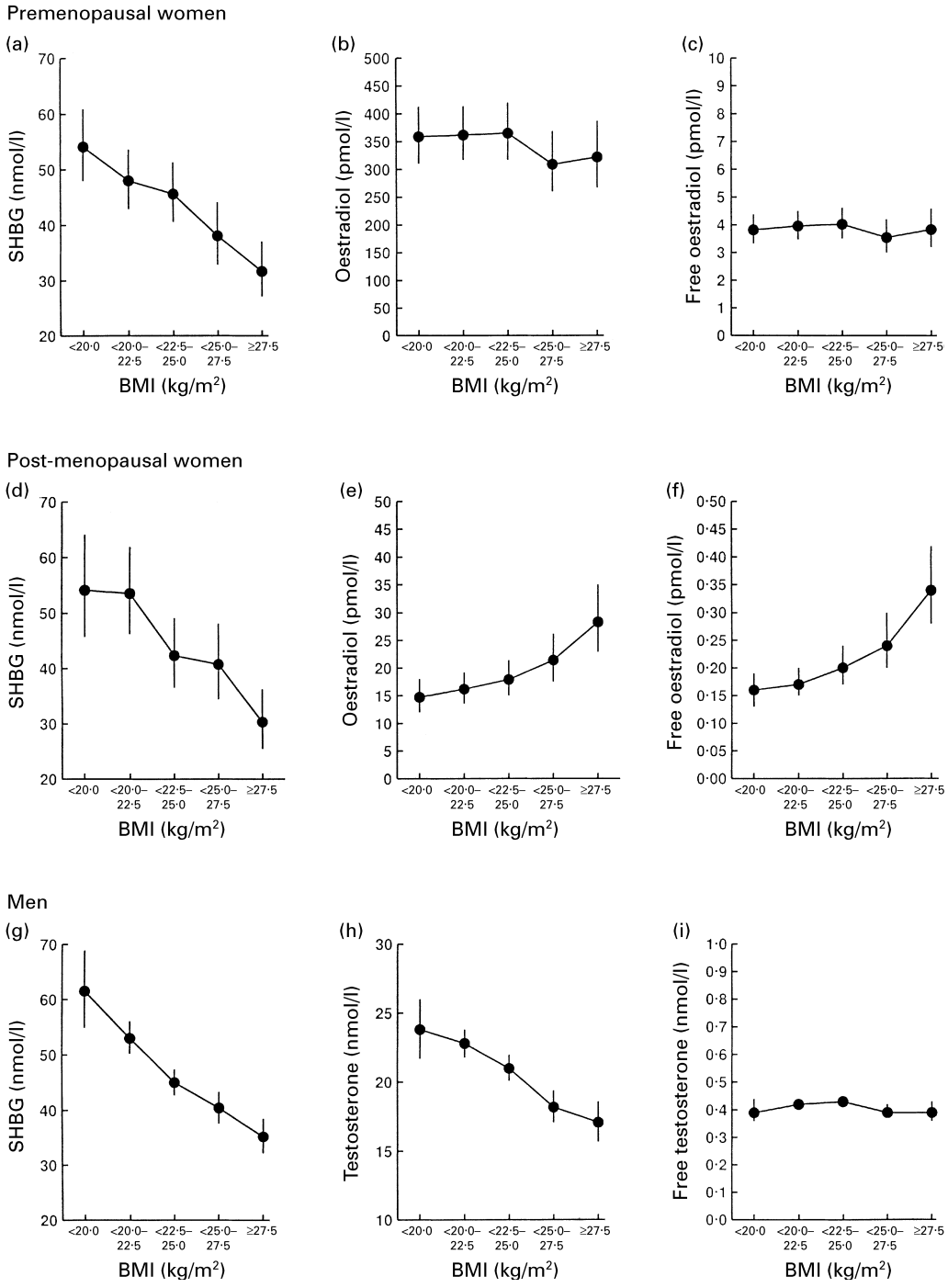

Fig. 1. Relationships between sex hormone-binding globulin (SHBG);a,d,g, oestradiol (b,e), free oestradiol (c,f), testosterone (h), and free testosterone (i) and BMI. Data for 636 premenopausal women, 456 post-menopausal women and 696 men from the European Prospective Investigation into Cancer and Nutrition, Oxford Centre (Thomas *et al.* 1999; Allen *et al.* 2000; Verkasalo *et al.* 2001). Values are means with their 95% confidence intervals represented by vertical bars.

Interpretation

Compared with the other cancer sites discussed, endometrial cancer appears to be much the most sensitive to sex hormones. This finding is compatible with the dramatic changes in endometrial cell behaviour during normal menstrual cycles, with high levels of mitotic activity occurring during exposure to oestradiol alone in the follicular phase, which are 'switched off' by progesterone during the luteal phase. In premenopausal women the large increase in risk for endometrial cancer associated with obesity may be explained by the high incidence of anovular menstrual cycles in obese women, and the consequent exposure to high levels of oestradiol unopposed by

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progesterone. In post-menopausal women the large increase in risk is again due to high levels of free oestradiol together with the normal very low levels of progesterone.

Breast cancer

Reproductive factors and sex hormones

Early age at menarche and late age at menopause increase breast cancer risk, indicating that longer exposure of the breasts to ovarian hormones increases the risk for breast cancer (Key & Pike, 1988*b*; Pike *et al*. 1993). Recent prospective studies have shown that among post-menopausal women those with relatively high oestradiol levels in their serum have a risk for breast cancer about 2·5 times higher than that of women with relatively low levels of oestradiol; few data are available for premenopausal women (Key & Verkasalo, 1999). Use of hormone-replacement therapy in post-menopausal women is also associated with a moderate increase in breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). It appears, therefore, that at least in post-menopausal women increased exposure to oestrogens does increase breast cancer risk. The role of progesterone is not clear, but the fact that the mitotic rate of breast epithelial cells is higher in the luteal phase than the follicular phase of the menstrual cycle suggests that progesterone may augment the mitotic effect of oestradiol, and hence that it might also increase breast cancer risk (Anderson *et al*. 1982; Key & Pike, 1988*b*).

BMI

The relationship between BMI and breast cancer risk is complex. In premenopausal women most studies have found either no association with risk or a weak inverse relationship (Ursin *et al*. 1995), although positive associations have been observed in countries with moderate or low rates of breast cancer (Pathak & Whittemore, 1992). The reduction in risk of premenopausal breast cancer associated with obesity is largely confined to early-stage disease; for example, in the large cohort of Norwegian women studied by Tretli (1989) there was a reduction in risk with increasing BMI for early-stage breast cancer, but not for late-stage breast cancer.

In post-menopausal women the risk for breast cancer increases with increasing BMI. The risk for post-menopausal women with a BMI of about 30 kg/m^2 is about 50 % higher than that among women with a BMI of about 20 kg/m^2 (Trentham-Dietz *et al*. 1997; Galanis *et al*. 1998). A marked increase in risk has been observed in relation to weight gain during adult life, perhaps because weight gained is likely to be mostly adipose tissue (Huang *et al*. 1997; Trentham-Dietz *et al*. 1997). The increase in breast cancer risk with increasing BMI is greater among women aged over 65 years than in younger post-menopausal women (Galanis *et al*. 1998). In a cohort study of 95 000 US nurses. Huang *et al*. (1997) reported that the increased risk for breast cancer associated with obesity in post-menopausal women was most evident among women who had never used hormone-replacement therapy, perhaps because obesity is a major determinant of oestrogen levels in these women, whereas in women who use hormone-replacement therapy this factor is the dominant determinant of oestrogen exposure.

Interpretation

In premenopausal women, overweight causes a reduction in SHBG and perhaps in total oestradiol, but has little if any effect on free oestradiol. Thus, overweight would not be expected to alter breast cancer risk, which is consistent with the observations from epidemiological studies that overweight does not increase risk in premenopausal women; the decrease in risk observed in many studies is not well understood, but could be partly due to an increase in the frequency of anovular cycles and reduced exposure to progesterone, and perhaps partly due to later diagnosis of tumours in obese women. In post-menopausal women obesity increases breast cancer risk, probably largely due to the high levels of free oestradiol.

Ovarian cancer

Reproductive factors and sex hormones

The risk of epithelial ovarian cancer increases with increasing age, although the rate of increase slows after about age 50 years. The fact that an attenuation in the increase in risk occurs at the time of menopause has prompted suggestions that sex hormones may have a direct role in its aetiology. However, data regarding the relationship between risk and age at menarche, age at menopause and hormone-replacement therapy have been inconsistent (Shu *et al*. 1989; Franceschi *et al*. 1991; Whittemore *et al*. 1992; Rodriguez *et al*. 1995; Banks *et al*. 1997).

The risk for ovarian cancer decreases with increasing parity and with increasing duration of oral contraceptive use, and there is evidence that prolonged breast-feeding also results in a decreased risk of the disease (Banks *et al*. 1997). Such evidence has been used in support of the 'incessant ovulation' theory of ovarian cancer pathogenesis (Fathalla, 1971; Casagrande *et al*. 1979). This theory hypothesizes that, since ovulation causes trauma to the ovarian epithelium and stimulation of mitoses, the more frequently a woman ovulates, the higher her risk of ovarian cancer. While ovarian cancer risk is associated with a woman's lifetime number of ovulations (Casagrande *et al*. 1979; Franceschi *et al*. 1982; Wu *et al*. 1988; Booth *et al*. 1989), such a finding is inextricable from the known risk-reducing effects of parity and oral contraceptive use. Furthermore, the reductions in risk associated with these factors are larger than might be predicted by this hypothesis on the basis of induction of anovulation alone. Alternative hypotheses include the theories that pregnancy acts by 'clearing' the ovary of cells which have undergone neoplastic transformation (Adami *et al*. 1994), or that ovarian cancer risk is associated with high levels of circulating gonadotrophins (for review, see Risch, 1998). Direct data regarding the relationship between endogenous hormone levels and ovarian cancer are very limited. In one small prospective study the risk of ovarian cancer decreased significantly

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($P < 0{\cdot}05$) with increasing follicle-stimulating hormone level, increased significantly ($P < 0{\cdot}05$) with increasing androstenedione level, and was unrelated to serum concentrations of progesterone, oestrone and oestradiol (Helzlsouer *et al*. 1995).

BMI

In the first large cohort study to investigate the issue, Lew & Garfinkel (1979) reported no consistent trend in the risk of death from ovarian cancer with increasing weight, but did observe a significantly ($P < 0{\cdot}05$) elevated risk of fatal ovarian cancer in women in the highest weight category compared with those of average weight. In a later US cohort study of 240 000 women, no significant relationship between fatal ovarian cancer and BMI was found (Rodriguez *et al*. 1995). In a prospective study in Iowa, Mink *et al*. (1995) showed no relationship between BMI and the risk of incident ovarian cancer (although they did observe elevated risks in women with a relatively high waist circumference:hip circumference).

Some of the larger population-based case–control studies have found significantly increasing risk of ovarian cancer with increasing weight (Casagrande *et al*. 1979; Polychronopoulou *et al*. 1993), 'obesity' (Irwin *et al*. 1991) or increasing BMI (Farrow *et al*. 1989; Purdie *et al*. 1995). However, most case–control studies have not found any relationship between body size and ovarian cancer (Hildreth *et al*. 1981; Franceschi *et al*. 1982; Koch *et al*. 1988; Hartge *et al*. 1989; Shu *et al*. 1989; Slattery *et al*. 1989; Herrinton *et al*. 1995).

In summary, the evidence regarding the relationship between usual adult BMI and ovarian cancer risk is conflicting, although there is little evidence that a high BMI might have a protective effect. The significant positive findings linking a larger body size with an increased risk of ovarian cancer in some studies mean that uncertainties about the relationship remain, and more prospective data are needed.

Interpretation

The role of hormonal factors in the aetiology of ovarian cancer is much less clear than it is for endometrial cancer and breast cancer. Risk appears to be associated in some way with ovulation, but the protective effects of both pregnancies and the oral contraceptive pill are stronger than can be explained simply by stopping ovulation. The association between BMI and ovarian cancer risk remains unclear, but there is no evidence that obesity in premenopausal women, which is definitely associated with anovulation, has a protective effect against this cancer.

Prostate cancer

Sex hormones

The principal androgen in men is testosterone, which is produced by the testes and converted within the main target tissues to dihydrotestosterone by 5α-reductase type II (Coffey & Isaacs, 1981). Dihydrotestosterone is the main functional intracellular androgen, crucial for the growth and development of the prostate gland, as it acts to stimulate prostatic cell proliferation and inhibit cell death. Experimental studies have shown that administration of testosterone can produce adenocarcinoma in the prostate gland of rats (Noble, 1977). Human studies have also suggested that higher circulating levels of free androgens, and in particular the metabolite androstanediol glucuronide, a serum marker of 5α-reductase activity and intra-prostatic dihydrotestosterone, may increase the risk of developing prostate cancer (Gann *et al*. 1996; Eaton *et al*. 1999).

BMI

The results of epidemiological studies of BMI and prostate cancer risk have been somewhat inconsistent (Nomura & Kolonel, 1991). The best data come from large prospective studies where selection and reporting biases are reduced or eliminated. In a prospective study of 135 000 Swedish construction workers Andersson *et al*. (1997) did not observe any significant association between BMI and the risk for incident prostate cancer, and similar broadly negative results have been reported from most other large prospective studies (Giovannucci *et al*. 1997; Lund Nilsen & Vatten, 1999). Severson *et al*. (1988) did observe some association between increasing BMI and prostate cancer risk, but suggested that this association might be accounted for more by lean tissue than by fat tissue. Two large prospective studies which looked at mortality as an end point did find a statistically significant ($P < 0{\cdot}05$) increase in mortality with increasing BMI, suggesting that obesity might reduce survival in men with prostate cancer (Lew & Garfinkel, 1979; Andersson *et al*. 1997).

Interpretation

According to the hypothesis that high levels of free testosterone increase the risk for prostate cancer, it would be expected that increasing BMI would have little if any effect on prostate cancer risk, and that risk might perhaps fall with severe obesity when free androgen levels are low. This interpretation appears to be consistent with the absence of a clear association between BMI and prostate cancer risk.

Conclusions

An excess of energy intake over energy expenditure leads to an increase in BMI and eventually to overweight and then obesity. These conditions can affect the risk for certain hormone-dependent cancers, but the nature of the relationship varies. In premenopausal women obesity causes an increase in the frequency of anovular menstrual cycles; this factor may explain the observed large increase in the risk for endometrial cancer, and perhaps the small decrease in breast cancer which has been observed in some studies. In post-menopausal women obesity causes an increase in serum concentrations of bioavailable oestradiol, and this factor causes increases in the risk for both endometrial cancer and breast cancer. These changes in sex hormone levels with BMI in women are not clearly associated with

the risk for ovarian cancer. In men increasing BMI has little effect on bioavailable androgen levels, and any effect of obesity on prostate cancer risk is small.

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