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Lifestyle and cancer of the reproductive organs

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Summary

The incidences of breast cancer, testicular cancer and prostate cancer are increasing in western societies. Concern has been expressed that human exposure to environmental xenobiotic compounds with endocrine activity may play a role in these phenomena, but supporting evidence for the existence of such a relationship is lacking. On the other hand, the twentieth century has seen profound changes in lifestyle, which have undoubtedly influenced the incidences of diseases.

The present report summarizes present knowledge on the relationship between hormone-dependent cancers in man and lifestyle determinants. Major lifestyle determinants related to reproductive cancer appear to be found in the areas of consumptive and reproductive behaviour. Specific determinants within these areas include caloric intake, physical activity, alcohol consumption, parity, exogenous hormone treatments, sexual activity and hygiene. Dramatic consumptive changes in the twentieth century with increased caloric intake in the presence of decreased physical activity, and increased alcohol intake and increased female smoking are thought to have promoted reproductive cancers. In addition, profound changes in reproductive behaviour with decreased parity, increased maternal age, increased sexual activity, wide application of various types of sex hormone therapy and contraceptive measures are thought to have contributed to increased reproductive cancer incidences.

Current knowledge on determinants of reproductive cancer suggests that lifestyle determinants may play a more prominent role than exposure to endocrine acting environmental xenobiotic compounds in the determination of trends in reproductive cancer incidences. However, data on human exposure to environmental endocrine active compounds are needed to allow an analysis of the actual risk of exposure to these compounds as regards reproductive organ cancer.

Samenvatting

De incidenties van borstkanker, testiskanker en prostaatkanker nemen in de westerse wereld toe. Er is sprake van zorg dat blootstelling van de mens aan stoffen in het leefmilieu met endocriene activiteit betrokken zouden kunnen zijn bij deze trends, maar ondersteunend bewijs voor een dergelijke relatie ontbreekt tot dusverre. Anderzijds heeft de twintigste eeuw diepgaande veranderingen in leefstijl te zien gegeven, die ongetwijfeld invloed hebben gehad op de incidenties van ziekten en aandoeningen.

Dit rapport vat de huidige kennis samen omtrent de relatie tussen hormoon-afhankelijke kankers bij de mens en leefstijldeterminanten. Belangrijke leefstijldeterminanten betrokken bij deze kankers worden gevonden op de gebieden van consumptief en sexueel gedrag. Specifieke determinanten daarbinnen zijn calorische inname, lichamelijke activiteit, alcoholconsumpotie, kindertal, hormoonmedicatie, sexuele activiteit en hygiëne. Ingrijpende consumptieve veranderingen in de twintigste eeuw zoals toegenomen calorische inname in samenhang met afgenomen fysieke activiteit, verhoogde alcohol consumptie en toename van roken door vrouwen worden verondersteld een rol te spelen bij de toename van kanker van de geslachtsorganen. Daarnaast hebben vergaande veranderingen in gedragspatronen rond de voortplanting, zoals verlaagd kindertal, hogere maternale leeftijd, toegnomen sexuele activiteit, brede toepassing van verschillende vormen van medicatie met geslachthormonen en vormen van contraceptie mogelijk bijgedragen aan toegenomen incidenties van kanker van de geslachtsorganen.

De huidige kennis omtrent determinanten van hormoon-gemedieerde kankers geeft aan dat leefstijldeterminanten een meer prominente rol lijken te spelen dan blootstelling aan stoffen met endocriene activiteit in het leefmilieu als het gaat om trends in de incidenties van deze vormen van kanker. Gegevens over humane blootstelling aan hormoonontregelaars in het milieu zijn echter nodig om een analyse te kunnen maken van het actuele risico van blootstelling aan deze stoffen met betrekking tot kanker van de geslachtsorganen.

1 Introduction

Within recent years increasing concern is being expressed about disturbances in human reproduction. Increasing trends in adverse reproductive effects in man in the twentieth century have been related to increased exposure to environmental contaminants with endocrine activity. Alleged effects of these so-called endocrine disrupters include decreased sperm quality, affected fertility, neurologic and immunologic effects, breast cancer and testicular cancer (Ashby et al., 1997). There are strong indications that effects on fertility and development in wildlife populations may be caused by substantial exposure to environmental contaminants which have certain endocrine activity. For the human population, not only is the relationship with exposure far from clear, in addition for many of the reproductive effects evidence for an increased incidence is lacking.

Over the past decades, several cancers of the reproductive organs, especially breast, testicular and prostate cancer, show an increasing incidence in the human population. As indicated above, these increases have been hypothesized to be related to endocrine disrupter exposure. Arguments for the existence of such a relationship are firstly the mechanistic plausibility of the idea that compounds with endocrine activity could interfere with tumors of endocrine-dependent organs, and secondly the experience in the past with the drug diethylstilbestrol, a synthetic estrogen which appeared causally related to cervix cancer. In spite of these arguments, a causal relationship between endocrine disrupters and human health effects is as yet far from proven. This is due in part to the scarcity of information on actual human exposure to endocrine disrupters, on their kinetics in the body, and on their relative contribution to endogenous endocrine activity. Moreover, besides the increased use of chemicals other profound changes in society have taken place over the last decades, which may have influenced the cancer trends mentioned. Many determinants that have been studied for these cancers relate to lifestyle factors. The relative contribution of lifestyle determinants to the incidence of reproductive organ cancers may outweigh the alleged role of endocrine disrupting xenobiotics In this study, we have reviewed the information available on lifestyle determinants in relation to cancer of the reproductive organs, in order to place the discussion on the contribution of endocrine disrupter exposure to these cancers into a wider perspective. Besides breast, testicular and prostate cancer, for comparison ovarian, endometrial and cervix cancer were studied as hormone-regulated cancers for which no time-related trend is evident.

The present study gives a general overview of current knowledge on the subject, with specific reference to available data on the Dutch population. Firstly, recent trends in the incidences of reproductive organ cancers are given, and an inventory is made of lifestyle and related endogenous determinants for each of these cancer types. Mechanistic aspects which may support causality of determinants are discussed. Secondly, data on current trends in relevant lifestyle determinants are collected. Finally, in a general discussion, the current knowledge on major lifestyle determinants of reproductive organ cancers is summarized. From this perspective the alleged role of endocrine disrupter exposure as suggested causative agents for the increases in cancer incidences is discussed.

2 Methods

Existing data were collected, initially from renowned standard databases, overviews and handbooks. For incidences and determinants of cancer we used: Cancer Epidemiology and Prevention (CEP), Schottenfeld and Fraumeni, 1996; Food, Nutrition and the Prevention of Cancer (FNPC), World Cancer Research Fund in association with American Institute for Cancer Research, 1997; Incidence of cancer in the Netherlands, Sixth report of the Netherlands Cancer Registration (NCR), Visser et al, 199; Volksgezondheid Toekomst Verkenning (VTV), Ruwaard, Kramers, 1993 and 1997; Nutritional Aspects of the Development of Cancer Committee on Medical Aspects (COMA), of Food and Nutrition Policy, 1998; and Signaleringsrapport Kanker 1999 (SRK), Nederlandse Kankerbestrijding, 1999.Data on demographic and lifestyle determinants were retrieved from: Centraal Buro voor de Statistiek (CBS), VTV and Bevolkingsvraagstukken in Nederland anno 1997, Nederlands Interdisciplinair Demografisch Instituut (NiDi), Van Nimwegen, Beets, 1997. Data from these sources were considered as being state of the art knowledge, and were reproduced in the present report without further scrutiny. However, more recent data in primary scientific literature were additionally considered. Although care was taken to balance the description of state of the art knowledge and of more recent data from primary scientific literature, this procedure may be a source of bias.

In general, four terms are used to denote the strength of scientific evidence of associations: convincing (evidence of a causal relationship is conclusive), probable (evidence is strong enough to conclude that a causal relationship is likely), possible (a causal relationship may exist, but the evidence is not strong enough to generate recommendations) and insufficient (suggestive evidence exists, but is too scarce or inconsistent to make judgements) (FNPC).

Mechanistic relationship flowcharts (chapters 3.#.3) were modelled according to VTV 1993, p.63. Within these charts, only apparent major lifestyle determinants are shown with their possible mechanistic relationship to the cancer type reviewed. For many determinants, although associations have been shown through epidemiological studies, causality has not been convincingly proven. There is a scarcity of mechanistic studies which could support causal relationships between determinants and cancer. In our charts, we have attempted to display in a simplified way mechanistic pathways that seem likely to explain the associations between major determinants and cancer. Three generalized mechanisms have been identified. Firstly, the term "DNA damage" points to adverse effects at the level of the genome in the widest sense. Secondly, "cell proliferation" relates to modulation of the mitotic activity of cells. Thirdly, "cell differentiation" pertains to effects on the maturation of cells. Generally speaking, the more mature or fully differentiated cells are, the lower is their mitotic capacity, and therefore differentiation induction will limit the proliferative capacity of cells, and decrease their potential of giving rise to tumours.

In this report, determinants are generally discussed in a qualitative way. Estimation of relative quantitative contributions of determinants to cancer incidence lies beyond the scope of this study. The contributions of determinants to cancer incidence is difficult to quantitate in view of considerable differences between study outcomes. Furthermore, most of the determinants of cancer are as yet unknown. The only prominent aspect of quantitation in this study can be found in the flow charts where only 'major' determinants have been collected as discussed in the accompanying text.

3 Incidence and Determinants

3.1 Breast cancer

3.1.1 Epidemiology

Breast cancer is the most common incident cancer in women and the third most common cancer overall. Worldwide, incidence and mortality rates are generally increasing, mostly in economically developed countries. This is also the case in The Netherlands (NCR) with a current incidence of around 1.3 in 1000 women (VTV) (figure 3.1.1. a). High risk areas include Europe, Australia and North America, whereas low incidence rates are reported in Asia and parts of Africa (figure 3.1.1.c). Populations that migrate from low- to high-incidence areas develop rates that approximate those of the new area within two generations, which indicates that lifestyle and environmental factors may be more important than genetic factors. Incidence of breast cancer increases with age (figure 3.1.1.b). Part of the worldwide increase is attributable to screening programs and aging of the population (SRK; CEP; VTV). Changes in lifestyle determinants, however, may also play a significant role.

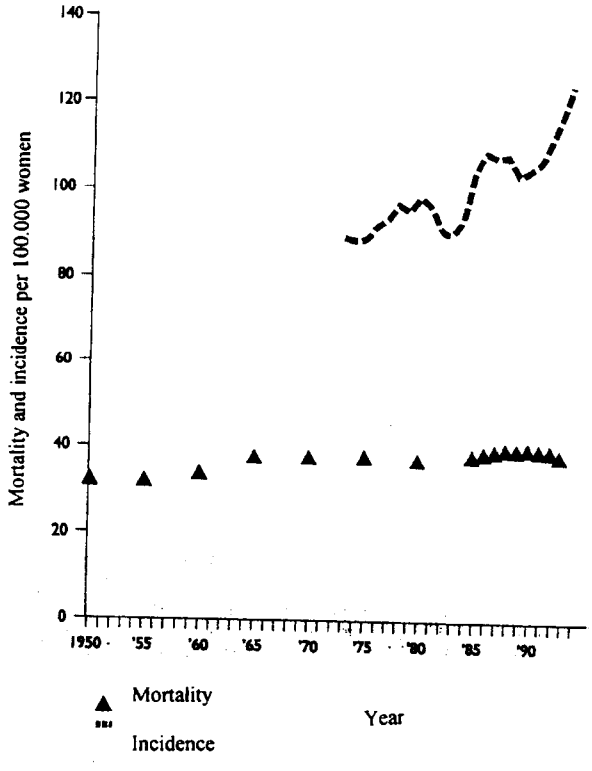

Figure 3.1.1. a: Breast cancer incidence and mortality in The Netherlands (SRK)

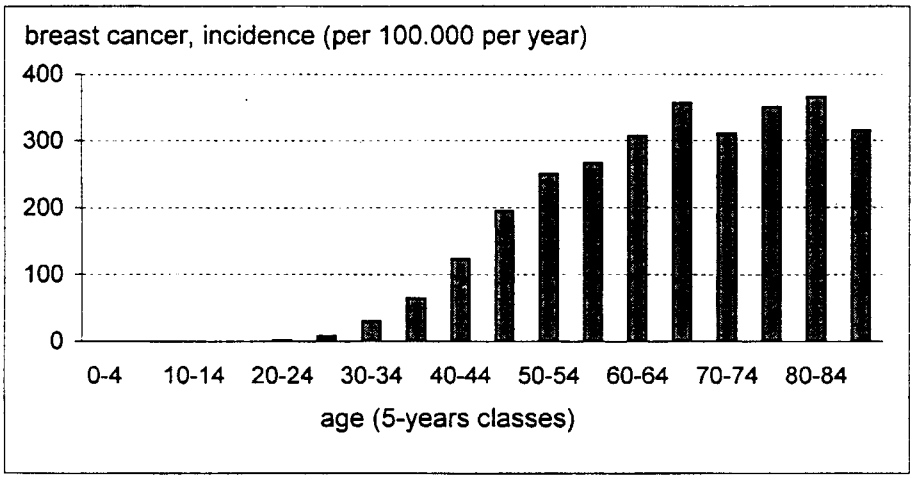

Figure 3.1.1. b: Age specific breast cancer incidence in The Netherlands (VTV)

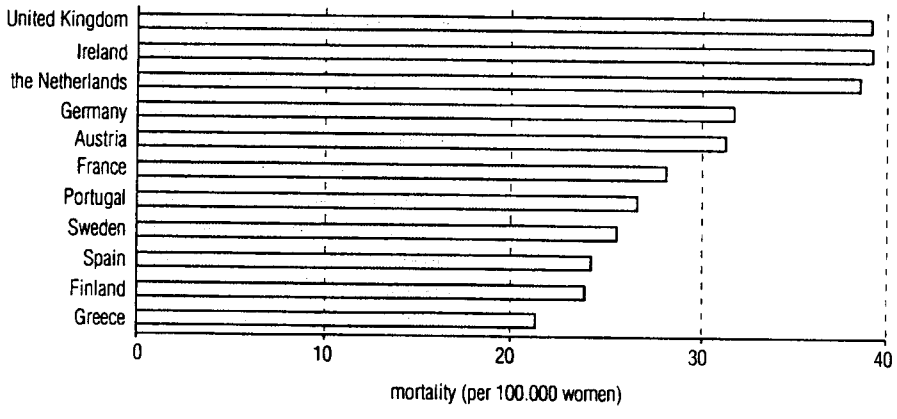

Figure 3.1.1. c: Breast cancer incidence by area (VTV)

3.1.2 Determinants

Many lifestyle and environmental determinants influence breast cancer incidence. An estimated 30-50% of all breast cancer cases can be attributed to the established risk factors. Of the remaining 50-70% of all cases, the origin of the disease is unknown (CEP; VTV). Determinants of breast cancer are reviewed below under six headings: hormonal exposure, nutrition, body size, physical activity and exogenous exposures.

Hormonal exposure

- Endogenous sex hormones
Epidemiologic, animal and experimental studies implicate an important role for estrogens in breast cancer etiology. Almost all of the known risk factors can be attributed to the cumulative exposure to bioavailable estradiol. Hormones involved in breast cancer etiology appear to be not genotoxic but affect the rate of cell division. Since estradiol stimulates cell growth and approximately 60% of all mammary tumors have estrogen receptors, estradiol is supposed to directly enhance mammary tumor growth. Case-control and correlation studies consistently reported higher estradiol levels in cases compared to controls and higher estrogen levels in American women (high risk) than in Asian women (low risk) (CEP). Animal studies show an increased incidence of mammary tumors after exogenous administration of estrogens (CEP).

The roles of progesterone and prolactin in breast cancer etiology remain unclear (CEP). There is no indication that progesterone is involved in the pathogenesis of breast cancer. However, progesterone may counterbalance the effect of estradiol, since pharmaceutical estrogens combined with progestins do not increase breast cancer risk, in contrast to preparations containing estrogens alone. Prolactin is important in animal breast cancer etiology but human studies are inconsistent.

- Menstrual cycle characteristics
Late natural menopause, early age at menarche, anovulatory cycles and short menstrual cycle length are established risk factors for breast cancer and may all be attributable to an increased cumulative exposure to bioavailable estradiol.
A two times increased risk is reported for menopausal age 55 or above compared to age 45 or lower (VTV; CEP; FNPC). Likewise, women with 40 or more years of menstrual activity have twice the risk of women with less than 30 years of menstrual activity (CEP). The decreased risk of early menopause may be attributable to cessation of ovarian function - which coincides with a drastic decrease in estradiol production - since women whose ovaria were removed showed a decreased risk (VTV).
A 30% increased risk is reported for menarchal age 11 or less compared to age 15 or above (VTV). In general, a 20% decrease in risk results from each year that menarche is delayed (CEP).
Not only age at menarche is a risk factor, also age when menstruation becomes regular seems to be a risk factor, since regular cycles reflect ovulatory cycles. An ovulatory cycle exists of two phases, the follicular (preovulatory) phase and the luteal (ovulatory) phase. The fact that the luteal phase coincides with high estradiol levels might explain the increased risk. Women who established regular cycles within 1 year after menarche had a two times increased risk compared to women with a 5-year or longer delay in onset of regular cycles. A fourfold increased risk was found for women with early menarche (age 12 or younger) and accelerated onset of regular cycles compared to women with late menarche (age 13 or older) and delayed onset of regular cycles (CEP). A prospective cohort study showed that women with irregular menstrual cycles had a significantly reduced risk (Den Tonkelaar and De Waard, 1996). Correlation studies show that the highest rates of regular (ovulatory) cycles are observed in populations with the highest breast cancer incidence (MacMahon et al, 1982).
Since long menstrual cycles have the same luteal phase as short cycles, women with short cycles are relatively more exposed to estrogen compared to women with longer cycle length. In low-risk countries longer menstrual cycles were reported than in high-risk areas and a retrospective study showed that the average cycle length of cases was significantly shorter compared to the controls (CEP).

- Reproduction
A two times increased breast cancer risk is observed among nulliparous women compared to women who have children (VTV; FNPC; CEP; COMA). Having a large number of children possibly decreases risk, although the main protective effect is associated with the first full-term pregnancy (VTV; CEP). Late age at first pregnancy (35 or above) increases risk three times compared to women who had children at age 18 or less (VTV; FNPC; CEP; COMA).
Long-duration breast feeding possibly decreases breast cancer risk. This decrease is generally not observed in populations in which long-duration nursing is not common (CEP; FNPC; COMA), although a 22% decreased risk was observed among premenopausal women (4-12 months breast feeding) (VTV).

- Exogenous estrogens
Most studies indicate that neither long-term nor short-term oral combination contraceptive use (estrogens combined with progestins) increase breast cancer risk (VTV; White E et al 1994). However, several studies in various countries have found an association between the duration of oral contraceptive use before the age of 25 and breast cancer risk (VTV; Pike et al.,1981, Mierik et al., 1986, Brenner et al., 1990, Ebeling et al., 1990, Johnson 1989, UK nAtl. Case Control Study Group, 1989, Olsson, 1989; White et al., 1994; Chie et al., 1998; Skegg and Spears, 1991, McPherson 1991).
Long-term postmenopause estrogen replacement therapy (10 years or over) increases risk with 30%. Estrogen replacement therapy in which estrogens are combined with progestagens are possibly not associated with increased risk, which may be due to the fact that progesterone counterbalances the effects of estrogen (VTV; FNPC).
Diethylstilbestrol (DES) use is not considered to be an important breast cancer risk factor (Waddell 1997, Golden 1998), although a slightly increased breast cancer risk has been observed (Calle EE ea, Am J Epidemiol 1996; 144(7): 645-652; Colton T ea 1993). In utero exposure to DES appeared not related to breast cancer risk (Weiss 1997, Hatch 1998). Continued surveillance is required since the in utero exposed women have not yet reached the age at highest risk (Hatch 1998).

Nutrition

- Fat and caloric intake
High fat intake, particularly total and saturated fat, is possibly associated with increased breast cancer risk (CEP; FNPC; VTV; COMA). Worldwide, fat consumption is highly correlated with breast cancer risk (CEP). On the other hand, COMA concludes that there is moderate evidence of no association (COMA). From animal experiments it became evident that fat intake is a determinant for mammary tumor formation (CEP; Tannenbaum, 1942; Welsh, 1992; Djuric, Kritschevsky, 1993). Three cohort studies failed to show an association between fat intake and breast cancer risk (Mills et al, 1989; Kushi et al, 1992; Willett et al, 1992), one cohort study showed a strong statistically significantly increased risk with total and saturated fat intake (Jones et al, 1987) and one cohort study reported a statistically significantly increased risk with saturated fat intake (Van den Brandt et al, 1993). Case-control studies generally produced either positive significant associations (La Vecchia et al, 1987; Hirohata et al, 1987; Van 't Veer et al, 1990) or no associations (Ferraroni et al, 1991; Graham et al, 1991). Hunter et al. (1996) found no evidence of a positive association between total dietary fat intake and the risk of breast cancer. They studied the pooled primary data of seven relatively high quality cohort studies.
Human experimental studies show that fat intake increases bioavailable estrogen (CEP; FNPC; Thorling, 1996; Rao, 1996). Thus, fat may exert its influence by increasing available energy as well as increasing bioavailable estrogen. In addition, dietary fat decreases cell-mediated cytotoxicity of T

lymphocytes, which increases tumor growth in general (Rao, 1996) and it was shown that low fat intake decreases the level of oxidative DNA damage, which is possibly associated with cancer risk in general (Djuric, Kritschevsky, 1993).
Increased energy-adjusted fat intake was found to be associated with accelerated menarche, which is an established risk factor for breast cancer (Merzenich et al, 1993).
There is no indication that unsaturated fat and cholesterol are associated with increased risk (FNPC).
Based on animal and human experimental studies, caloric intake is probably associated with mammary tumor growth. Few epidemiologic data are available for this item. A positive association between childhood energy intake and adult cancer risk was shown in a cohort study (follow up study, data collected in a survey during 1937-1939) (Frankel et al. 1998). Indirect evidence comes from animal studies. Decreased intake of calories results in a markedly decreased incidence of mammary gland tumors in rodents (Weindruch 1992; Masoro 1993). Human experimental and animal studies show that caloric intake is highly associated with bioavailable estrogen levels, oncogene expression, oxidative DNA damage and, evidently, energy status and inversely associated with antioxidant enzyme activity and DNA repair (CEP; Weindruch 1992; Kritchevsky 1995; Djuric Z et al. 1993). Caloric restriction was shown to decrease insulin-like growth factor IGF-1, which modulates cell proliferation, apoptosis and tumorigenesis. IGF-1 increases bioavailable estradiol levels, which, in turn, increases cancer risk. An animal study showed that IGF-1 is a possible key factor in tumorigenesis, since tumor formation in calorie-restricted IGF-1-restored rats was comparable to ad libitum fed rats and increased compared to calorie-restricted rats (Dunn et al. 1997).
In conclusion, the hypothesized influence of high caloric intake and/or high fat consumption on mammary tumor growth seems related to the effects on bioavailable energy and estradiol levels. The effects of caloric restriction are generally more pronounced than that of low-fat diets (Djuric et al. 1993; Kritchevsky 1995).

- Foods of plant origin
Vegetables and fruits are possibly protective against breast cancer (FNPC; COMA). In two case-control studies, consumption of vegetables and fruits was correlated with a decreased risk (Freudenheim et al, 1996; La Vecchia et al, 1987). No associations or nonsignificant decreases were reported in one cohort and two case-control studies (Rohan et al, 1993; Van 't Veer et al, 1990; Richardson et al, 1991).
Dietary fibre is possibly protective against breast cancer. Worldwide, dietary fibre intake is highly inversely correlated with breast cancer incidence (FNPC). Most case-control and cohort studies report a decreased risk (FNPC; CEP). Animal experiments show protective effects of dietary fibres as well (FNPC; CEP). Dietary fibres and grain were shown to decrease estradiol levels in human experimental studies (Thorling, 1996).
Phytoestrogens are possibly protective against breast cancer (FNPC; COMA). Ecologic, epidemiologic, animal and in vitro studies generally report a protective effect of phytoestrogens (plant food ingredients with estrogenic activity) and soy products. A relatively low incidence of breast cancer is observed in populations consuming relatively large amounts of soy (CEP; FNPC; Kurzer, Xu, 1997; Horn-Ross, 1995; Adlercreutz, 1995). Case-control studies report that high urinary phytoestrogen levels were associated with a nearly 70% reduction in risk (Ingram et al, 1997; CEP; FNPC; Kurzer, Xu, 1997; Horn-Ross, 1995; Adlercreutz, 1995). In animal and in vitro experiments, phytoestrogens inhibited mammary carcinogenesis or reduced tumor growth (CEP; FNPC; Kurzer, Xu, 1997; Horn-Ross, 1995; Adlercreutz, 1995). Phytoestrogens competitively suppress estradiol binding to the estradiol receptor (ER). Moreover, phytoestrogens were shown to increase synthesis of SHBG, which binds bioavailable estradiol, thus decreasing breast cancer risk

(Horn-Ross, 1995; Adlercreutz, 1995). Genistein, a soy phytoestrogen, inhibits growth of both ER-negative and ER-positive human breast cancer cell lines (Kurzer, Xu, 1997; Horn-Ross, 1995; Adlercreutz, 1995). Soy products were shown to prolong menstrual cycles and decrease concentrations of reproductive hormones, both inversely associated with breast cancer risk, in premenopausal women (Kurzer, Xu, 1997). Finally, phytoestrogens possess antioxidant action in vivo and in vitro (Kurzer, Xu, 1997).

- Micronutrient intake
Epidemiologic data indicate a weak protective effect of carotenoids, which might be explained by its antioxidant defense (FNPC; CEP). There is no indication that retinol and vitamin E are associated with breast cancer risk. Evidence of an association between vitamin C, vitamin D or selenium and mammary tumor growth is insufficient (FNPC).

- Coffee and alcohol
Epidemiologic studies (cohort and case-control) consistently showed no relationship between coffee consumption and breast cancer risk (FNPC).
Most epidemiologic (cohort and case-control) studies report a significantly increased risk with increased alcohol intake (FNPC; CEP). The summary data suggest that consumption of three or more alcoholic drinks per day increases risk with 50-70% compared to no drinks (CEP). Animal experiments showed that alcohol enhances mammary carcinogenesis (FNPC).

Body size

- Weight
A strong relationship exists between weight and breast cancer risk in postmenopausal women. This association might be explained by the fact that almost all postmenopausal endogenous estrogen is produced in adipose tissue. For premenopausal women, data from epidemiologic studies are somewhat inconsistent, although it is generally accepted that premenopausal weight gain might be a risk factor (CEP; VTV; FNPC). Recently a population-based case-control study among Asian-Americans was published in which adult adiposity was found to be an important determinant of breast cancer risk (Ziegler et al, 1996). Obesity in childhood and adolescence accellerates biological maturity (Thorling, 1996). Since obesity leads to a decreased age of menarche and increased estrogen levels, both of which are established risk factors, body weight is a likely determinant for breast cancer (Matkovic et al, 1997). The distribution of body fat did not seem to contribute to breast cancer risk (CEP).

- Height
Epidemiologic studies (including cohort studies) consistently showed significant positive associations between height and breast cancer risk (FNPC; Van den Brandt et al, 1997). Li ea reported that not total height but the age when maximum height was reached did affect risk (Li et al, 1997). Rapid early growth is associated with early menarche and early age when maximum height is reached and probably with increased caloric intake, which explains that rapid early growth increases risk (FNPC).

Physical activity

The evidence that physical activity decreases breast cancer risk is convincing (FNPC; CEP). Epidemiologic studies consistently report a 60-70% decrease of risk among active women compared to inactive women (FNPC; CEP). Data from animal studies are in agreement with this finding

(FNPC; CEP). One animal study reported no difference in mammary tumor incidence between exercised rats and calory-restricted rats, which indicates that energy balance is, at least in part, responsible for the protective effect (Hoffman-Goetz, Husted, 1994).
Moderate regular physical activity delays menarche and may lead to anovulatory cycles, both factors that decrease risk (Merzenich et al, 1993; Bernstein et al, 1987; Hoffman-Goetz, Husted, 1994). Indeed, exercise was shown to influence hormone metabolism, resulting in decreased estrogen levels (Hoffman-Goetz, Husted, 1994).
Physical activity influences the immune system (animal and human experimental studies), but to what extent the immune system is involved in breast cancer etiology is uncertain (Hoffman-Goetz, Husted, 1994).

Exposures

- Cigarette smoking
Evidence that a relationship exists between cigarette smoking and breast cancer is insufficient (CEP; FNPC). Both a decreased risk, due to an anti-estrogenic effect, and an increased risk have been reported (CEP; FNPC).

- Ionising radiation
Relatively high exposures to ionising radiation increase breast cancer risk, particularly when exposure occurs before age 30 (FNPC; VTV). Since high exposures are not common, this determinant is a minor contributor to overall breast cancer rates (FNPC; VTV).

Environmental chemicals

Higher levels of PCBs and the DDT metabolite DDE were found in cases compared to controls. Other well-conducted studies, however, failed to confirm these findings (FNPC; Golden et al, 1998). Therefore, the evidence to date shows no association between exposure to PCBs or DDE and increased breast cancer risk (Golden et al, 1998).
It is unclear whether or not endocrine disrupting chemicals affect breast cancer risk. Theoretically, an effect of environmental endocrine modulators is possible (Kavlock et al, 1996), but biological plausibility alone is not sufficient for concluding that these chemicals have indeed adverse health effects (Golden et al, 1998). Moreover, the supposed effects of endocrine disrupting chemicals are not established in humans (Ashby et al, 1997; Mennes and Piersma, 1996; Golden et al, 1998; Waddell, 1998). DES use, on the other hand, is a minor breast cancer risk factor (see above) and is in a way the cause of the concern about endocrine disrupting chemicals for the human population. However, effects of DES only occur at massive doses and since exposure to environmental endocrine modulators is probably very low (Safe, 1995; Waddell, 1998; Mennes and Piersma, 1996), it appears to be unlikely that environmental exposure to endocrine active compounds would be sufficient to cause adverse effects. Overall, an association between exposure to environmental endocrine modulators and breast cancer risk seems unlikely, but more research on human exposure and effect relations is certainly required.

Other determinants

- Benign breast disease
Benign breast diseases associated with epithelial changes were shown to increase breast cancer risk (CEP; VTV). Whether an association exists between fibrocystic disease and fibroadenoma and

breast cancer risk is uncertain. Both a twofold increased risk (CEP) and no association were reported (VTV).

3.1.3 Mechanistic Summary

In a great majority of cases breast carcinoma develops in the ductal epithelium. The interrelationship between the various determinants and their mechanistic connection to breast cancer can be summarized as follows (Figure 3.1.2.).

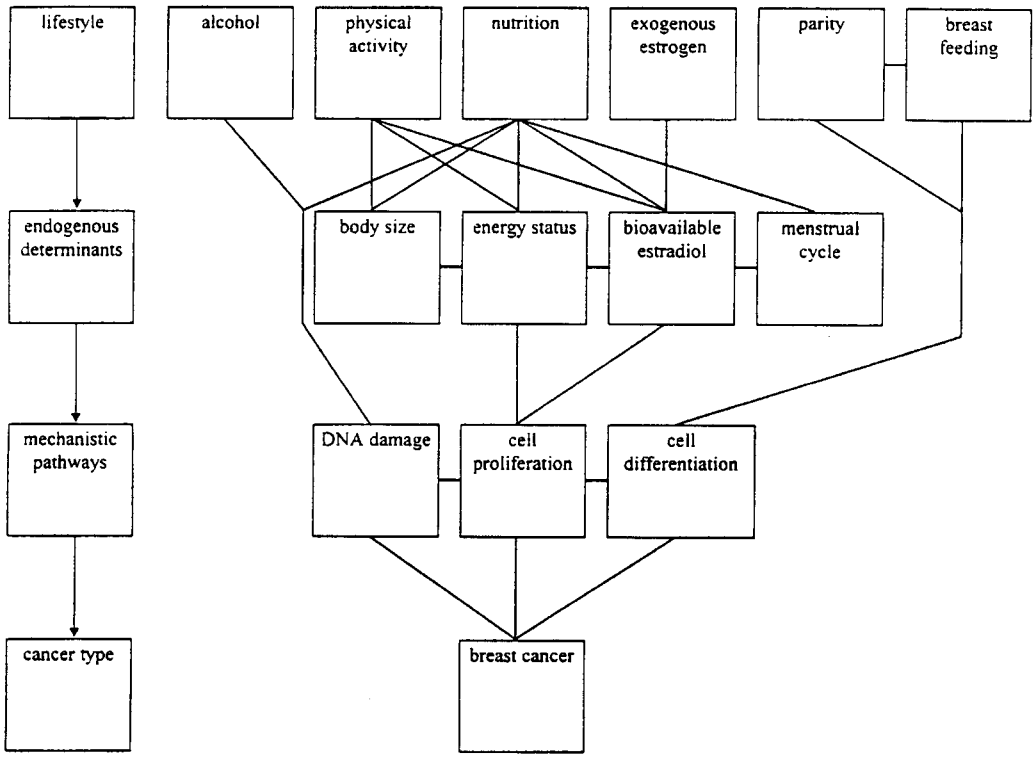

Figure 3.1.2: Mechanistic interrelationship between major lifestyle determinants of breast cancer

Alcohol interferes with DNA integrity. Nutritional energy intake correlates with oxidative DNA damage, through an inverse correlation with antioxidant enzyme activity. On the other hand antioxidant components in food may protect against oxidative DNA damage.

Cell proliferation of mammary tumor cells appears to be mainly regulated via energy status and bioavailable estradiol levels. Moreover, energy status influences estradiol levels via the insulin pathway (figure 3.1.3). Cumulative exposure to bioavailable estradiol, which is defined as free hormone not bound to sex hormone binding globulin (SHBG), links most of the established risk factors. The biochemical mechanism by which determinants influence bioavailable estradiol metabolism has been investigated in several experimental studies. In short, bioavailable estradiol may bind either to the estrogen receptor, thus stimulating cell proliferation, or to SHBG, followed by conversion into an inactive metabolite. Increased SHBG levels therefore result in decreased bioavailable estradiol levels. SHBG synthesis is increased by physical activity, caloric restriction and phytoestrogens and is decreased by insulin.

Caloric intake ↓
→ Insulin ↓ → IGFBP-1 ↑ → IGF-1 ↓ → SHBG ↑ → bioavailable estradiol ↓
Physical activity ↑

SHBG = sex hormone binding globulin
IGFBP-1 = insulin-like growth factor binding protein
IGF-1 = insulin-like growth factor

Figure 3.1.3: Regulation of bioavailable estradiol by energy status (caloric intake and physical activity)

Nutrition and physical activity are highly correlated with energy status and therefore with body size and estradiol levels. Fat and caloric intake directly increase bioavailable energy. Phytoestrogens decrease free estrogen levels via stimulation of SHBG-synthesis.
Endogenous estrogen levels are determined to a large extent by menstrual cycle characteristics, which are influenced by nutrition. High energy status leads to an earlier menarche, which, in turn, increases estrogen exposure. Phytoestrogens prolong cycle length, resulting in a lower lifetime estrogen exposure.
Exogenous estrogens not combined with progestagens increase cell proliferation. Both contraceptives and menopause therapeutics account for high exogenous estrogen exposures. Progestagens, which are present in modern contraceptive drugs, neutralize the stimulating effect of estrogen on cell proliferation, as suggested by epidemiologic studies. Progesterone decreases the number of estrogen receptors and increases the activity of enzymes that metabolize bioavailable estrogens into inactive metabolites.
More recents findings indicate that contraceptive use below the age of 25 is associated with increased breast cancer risk. This may relate to the fact that in this age group mammary epithelium is developing and has a highly proliferative status. During this period the exposure to relatively high estrogen levels may preclude cells from complete differentiation and increase the risk of tumor development later in life. In support of this possible mechanism, Anderson et al. (1989) described an increased epithelial proliferative activity in breast biopsies from nulliparous oral contraceptive users as compared to nonusers. In addition, in young oral contraceptive users Ollson et al. (1987) observed changes in plasma prolactin and breast estrogen receptor concentration similar to what is seen in breast cancer patients.
Cellular differentiation of the mammary epithelium occurs mainly during puberty as the mammal glands develop. Further maturation occurs during pregnancy and when mammary tissue becomes functional after childbirth. The inverse association of parity and total breast feeding time with breast cancer incidence is probably attributable to differentiation-inducing effects of these determinants, which decreases the proliferative potential of mammary epithelial cells.

3.2 Ovarian Cancer

3.2.1 Epidemiology

Ovarian cancer is the seventh most common cancer in women and may affect almost 2% of the female population over lifetime. Although not as common as breast cancer, ovarian cancer is an important contributor to cancer mortality due to its high fatality rate. Five-year survival rates are less than 30%. The highest incidence rates are found in white women in Europe and North America. The Netherlands have stable incidence rates of around 10 in 100.000 women (figure 3.2.1. a) (NCR), which is comparable to surrounding European countries. Low rates are reported in Asia and Central and South America. In most high risk areas, ovarian cancer incidence remained constant for decades, whereas previously low incidence rates in Asia are now increasing. Ovarian cancer incidence increases with age and is rare in young women (figure 3.2.1. b). Women of Asian descent who reside in high risk areas have higher incidence rates compared to their Asian counterparts, which indicates that lifestyle and environmental factors may be important ovarian cancer determinants.

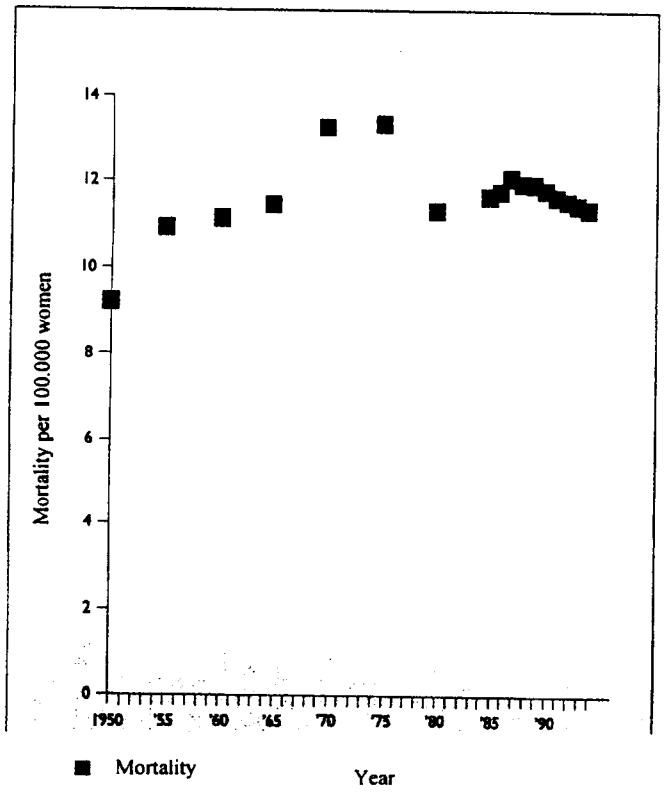

Figure 3.2.1. a: Ovarian cancer mortality in The Netherlands (SRK)

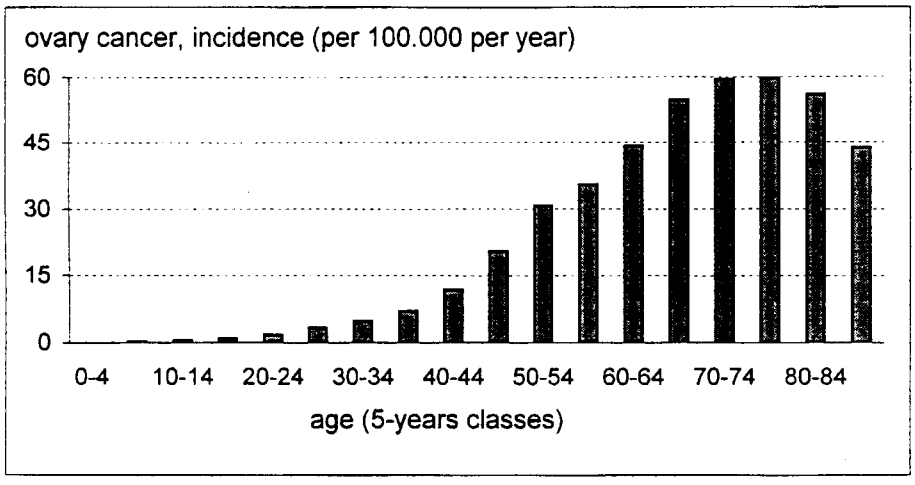

Figure 3.2.1. b: Age specific ovarian cancer incidence in The Netherlands (VTV)

3.2.2 Determinants

Lifestyle factors are known to contribute to ovarian cancer incidence, but few specific determinants have been established.

Hormonal exposure

- Endogenous sex hormones
Animal studies indicate that elevated levels of gonadotropic hormones promote growth of ovarian carcinoma by induction of tumor angiogenesis (Schiffenbauer et al, 1997). Indeed, elevated levels of gonadotropins are found in ovarian cancer patients (Schiffenbauer et al, 1997).
Indirect data suggest that prenatal exposures to exogenous or high endogenous estrogens increase germ cell tumor risk. However, since estrogen was shown to inhibit ovarian tumor growth, the evidence to date is insufficient to establish the suggested association (CEP).

- Reproduction
A consistently decreased risk is reported for parous women compared to nulliparous women. Risk substantially decreases with the number of pregnancies (CEP; FNPC; Westhoff, 1996; COMA). The protective effect of pregnancy may be attributed to the strong decrease of pituitary gonadotropin secretion (CEP; Hulka, 1997; COMA) or to inhibition or suppression of another aspect of ovarian function (Westhoff, 1996).
Theoretically, breast-feeding would be protective against ovarian cancer due to postponement of resumed gonadotropin secretion. Epidemiologic data, however, are not consistent (CEP).
Indirect evidence exists that infertility is associated with a slightly increased ovarian cancer risk (CEP; COMA).

- Menstrual cycle characteristics
Epidemiologic data suggest that no association exists between age at menarche and menopause and ovarian cancer risk (CEP).

- Exogenous estrogens
Administration of estrogens was shown to prevent the development of ovarian tumors in animal studies (CEP). Human studies consistently show a protective effect of oral contraceptive use against ovarian cancer (CEP; FNPC; Cuzick, 1996; La Vechhia et al, 1996; COMA). The decreased risk increases with duration of use (Westhoff, 1996) and may be attributed to the fact that exogenous estrogen reduces pituitary gonadotropin secretion (CEP; Hulka, 1997) or to reduction of the number of ovulations.
There is no indication that postmenopause estrogen replacement therapy is associated with ovarian cancer risk (CEP). Infertility treatment probably increases ovarian cancer risk, particularly treatment with human menopausal gonadotropin (hMG) (Shushan et al, 1996; CEP). Most studies reported an increased risk among infertile women who used ovulation-induction drugs compared to infertile women who did not use fertility drugs (CEP). Since recent data are inconsistent with this finding (Venn et al, 1995; Westhoff, 1996), additional studies are required. Fertility drugs stimulate production of gonadotropin hormones, therefore, an effect would indeed be likely (Hulka, 1997).

Nutrition

At present no evidence exists that any dietary factors influence ovarian cancer risk (FNPC; CEP; COMA). The few data available report a protective effect of vegetable fibre intake, but more research is required (FNPC; CEP; Verhoeven et al, 1996; COMA). Theoretically, consumption of galactose, a component of lactose, may affect ovarian cancer risk, since galactose influences gonadotropin metabolism (CEP). However, epidemiologic data do not support this hypothesis. Neither coffee nor alcohol consumption seems to be associated with ovarian cancer risk (CEP).

Body size

Data regarding the association between body weight and ovarian cancer are inconsistent (CEP; FNPC), although ovarian cancer risk appears to be independent of obesity.
The few data available are insufficient to establish whether height and ovarian cancer are related (CEP).

Exposures

- Ionising radiation
High doses of ionising radiation probably induce ovarian cancer, as suggested by a study amongst Japanese atomic bomb survivors (Tokuoka et al., 1987). The relatively small amounts of radiation to which women are usually exposed should have little effect on ovarian cancer development (CEP).
- Asbestos
An association between asbestos and ovarian cancer is not likely. Several cohort studies indicated that occupational or industrial exposure to high asbestos levels increased ovarian cancer incidence, however, pathologists showed that the lesions diagnosed as ovarian tumors are probably mesotheliomas (tumors caused by asbestos exposure) that incidentally involve the ovary (CEP). Exposure to asbestos is generally very low, therefore, even if an association would exist, additional risk for ovarian cancer would be negligible.

- Talc powder
Talc granules have often be detected in ovarian tumors and only occasionally in normal ovarian tissue. In addition, most studies have shown an increased risk for women who reported regular perineal use of talc powder. Animal studies are consistently negative regarding the carcinogenicity of talc. Therefore, talc possibly increases ovarian cancer risk, but more research is required.
- Cigarette smoking
Epidemiologic studies have generally failed to show an association between tobacco smoking and ovarian cancer risk (CEP).

Endocrine disrupting chemicals

No data are available regarding the influence of environmental chemicals.

Infectious agents

There is no indication that ovarian infection by any microorganism is associated with ovarian cancer (CEP).

3.2.3 Mechanistic Summary

Ovarian neoplasms may arise in germ cells orfollicular epithelial cells but originate mostly in epithelial cells. The interrelationship between the various determinants and their mechanistic connection to ovarian cancer is summarized in Figure 3.2.2.

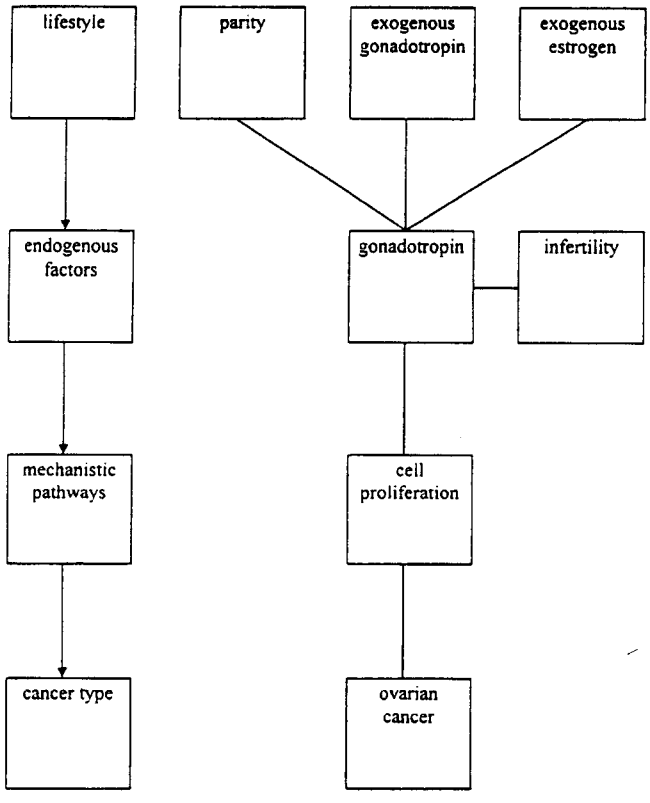

Figure 3.2.2. Mechanistic interrelationship between major lifestyle determinants for ovarian cancer

Ovarian cell proliferation is stimulated by gonadotropin hormone exposure. Most determinants of ovarian cancer can be linked to gonadotropin levels. Both oral contraceptives and pregnancy decrease gonadotropin levels and are protective against ovarian tumors. Conversely, infertility treatment increases gonadotropin levels as well as ovarian cancer risk.

3.3 Endometrial Cancer

3.3.1 Epidemiology

Endometrial cancer is the most common gynecologic cancer, but is usually not fatal. Mortality rates have been declining during the past decades, which is probably due to earlier detection and improved classification and treatment. Endometrial cancer incidence is high in economically developed countries. Highest incidence rates are reported in North America and Europe, low rates are found in Asia and Africa. Similar to other European countries the incidence rates in The Netherlands are stable at 10 in 100.000 women (figure 3.3.1. a) (NCR). Incidence rates are generally higher in white than in black women. Since incidence is higher in white, black and Asian women in the United States compared to their racial counterparts in lower risk areas, lifestyle and environmental factors may be important determinants. Endometrial cancer incidence increases with age (figure 3.3.1. b).

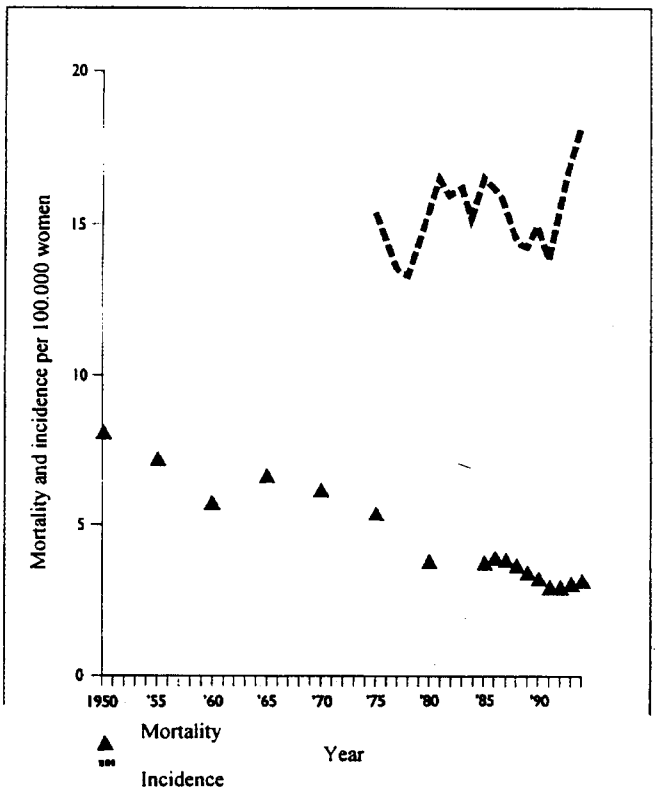

Figure 3.3.1. a: Endometrial cancer incidence and mortality in The Netherlands (SRK)

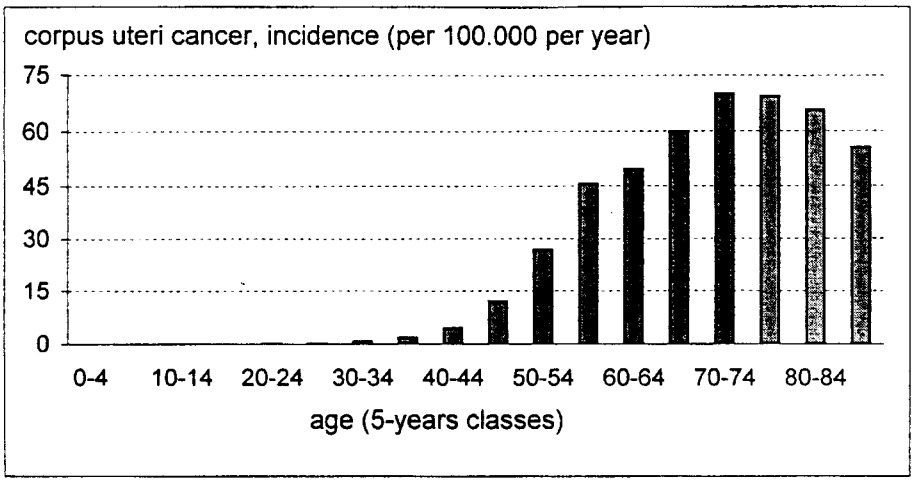

Figure 3.3.1. b: Age specific endometrial cancer incidence in The Netherlands (VTV)

3.3.2 Determinants

Endometrial cancer determinants include hormonal exposure, nutrition, body size and genetic predisposition.

Hormonal exposure

- Endogenous sex hormones
Similar to breast cancer, endometrial cancer is highly associated with relatively high estrogen levels or prolonged exposure to high estrogen levels (FNPC). Most case-control studies show that cases have higher serum estrogen levels compared to controls (CEP).
More clearly than for breast cancer, progesterone antagonizes the effect of estrogen. Progesterone decreases the number of estrogen receptors and increases the activity of enzymes that metabolize bioavailable estrogens into inactive metabolites. Case-control and cohort studies consistenly show that estrogen therapy combined with progestins reduce the increased endometrial cancer risk caused by therapy with estrogens alone. Moreover, endometrial cancer and endometrial hyperplasia, which is caused by high estrogen levels and may be a precursor of endometrial cancer, can be treated with progestagens (CEP).

- Reproduction
Case-control studies consistently showed that nulliparity is associated with a two- to threefold increased endometrial cancer risk and that risk decreases with increasing number of children (CEP; FNPC; McPherson et al, 1996; COMA). No association was reported for age at first birth and endometrial cancer risk (CEP). Infertility possibly increases risk, particularly when infertility is caused by progesterone deficiency (CEP; Sulak, 1997).

-Menstrual cycle characteristics
Late age at menopause and early age at menarche are established endometrial cancer determinants, as well as a relatively long ovulation span (years between menarche and menopause) (CEP;

McPherson et al, 1996). The increased risk may be attributable to an increased cumulative exposure to bioavailable estradiol.

- Exogenous estrogens
Oral combination contraceptive use (estrogens combined with progestagens) drastically decreases endometrial cancer risk (CEP; FNPC; Sulak, 1997; La Vecchia et al, 1996). The protective effect is dose-related and persists for years after discontinuing use (CEP; Stanford et al, 1993). Oral contraceptives in which estrogen was not combined with progestagen were shown to increase risk and were therefore removed from the market (Cuzick 1996, CEP).
Case-control and cohort studies consistently show that postmenopause estrogen replacement therapy (without progesterone comedication) increases risk (CEP). The increased effect is related to dose and duration of therapy and remains for years after discontinuing use (CEP; Green et al, 1996).

Nutition

- Fat intake
Fat intake is possibly associated with endometrial cancer risk (CEP; FNPC; COMA), although the evidence is considered insufficient (FNPC; COMA). Ecologic and case-control studies have shown an association between high fat consumption and endometrial cancer risk (CEP; FNPC; Goodman et al, 1997). An increased risk may be attributed to the fact that fat increases bioavailable estrogen levels. Human experimental studies and studies concerning vegetarians and non-vegetarians show that high fat intake elevates estrogen levels (CEP; FNPC; Thorling, 1996; Rao, 1996). In addition, high fat consumption increases obesity, which is a known endometrial cancer determinant (CEP; FNPC; COMA). The effect of fat intake appears to be independent of the effects of obesity and caloric intake (FNPC).
The few data available suggest that cholesterol increases endometrial cancer risk, but more research is required (FNPC; Goodman et al, 1997; COMA).

- Cereals, vegetables and fruits
Intakes of cereals, vegetables and fruits, particularly those high in lutein, were inversely correlated to endometrial cancer risk (FNPC; Goodman et al, 1997; COMA). The protective effect may be due to the phytoestrogen content, since phytoestrogens decrease bioavailable estradiol levels by increasing sex hormone binding globulin (SHBG).

- Other dietary factors
There is no indication that alcohol consumption is associated with endometrial cancer risk (CEP; FNPC).

Body size

- Weight
Case-control and cohort studies show a strong association between body weight and endometrial cancer risk in pre- and postmenopausal women(CEP; FNPC; COMA). Risk is two- to tenfold increased among obese women compared to women with normal weight (CEP; FNPC; Goodman et al, 1997). In many high risk areas, obesity is considered as the major cause of endometrial cancer (CEP; COMA). The distribution of body fat did not seem to contribute to endometrial cancer risk (FNPC). The biochemical mechanism by which obesity elevates risk may be an increased conversion of androstenedione into estrone in adipose tissue and a decreased synthesis of sex hormone binding globulin (SHBG).

Physical activity

The few data available suggest an inverse correlation between physical activity and endometrial cancer risk, but more research is required (Goodman et al, 1997).

Exposures

- Cigarette smoking
Smoking was consistently reported to be protective (CEP). The reduced risk has been attributed to the suggested anti-estrogenic effect of cigarette smoking (CEP). In addition, smoking decreases the age at menopause, which decreases endogenous estrogen exposure.

Environmental chemicals

There is no indication that environmental chemicals, like endocrine disrupting compounds, influence endometrial cancer risk (Waddell, 1998).

Other determinants

Women with diabetes or abnormal glucose intolerance show an increased endometrial cancer risk (CEP). Although this increased risk may be explained by the fact that high insulin levels result in high bioavailable estradiol levels (figure 1.4), thus increasing endometrial cancer risk, body weight is probably a confounding factor for both diabetes and endometrial cancer. Therefore, more research is required to establish whether the increased risk among women with diabetes is at least partly due to obesity (CEP). Likewise, it has been reported that hypertension and gallbladder disease were associated with endometrial cancer risk. Obesity and estrogen use are important risk factors for all three diseases and in studies that adjusted for these confounding factors, no associations were found (CEP).

3.3.3 Mechanistic Summary

Most cancers of the uterus arise in endometrial lining, although they may also occur in the myometrium. The interrelationship between the various determinants and their mechanistic relation to endometrial cancer can be summarized as follows (Figure 3.3.2).

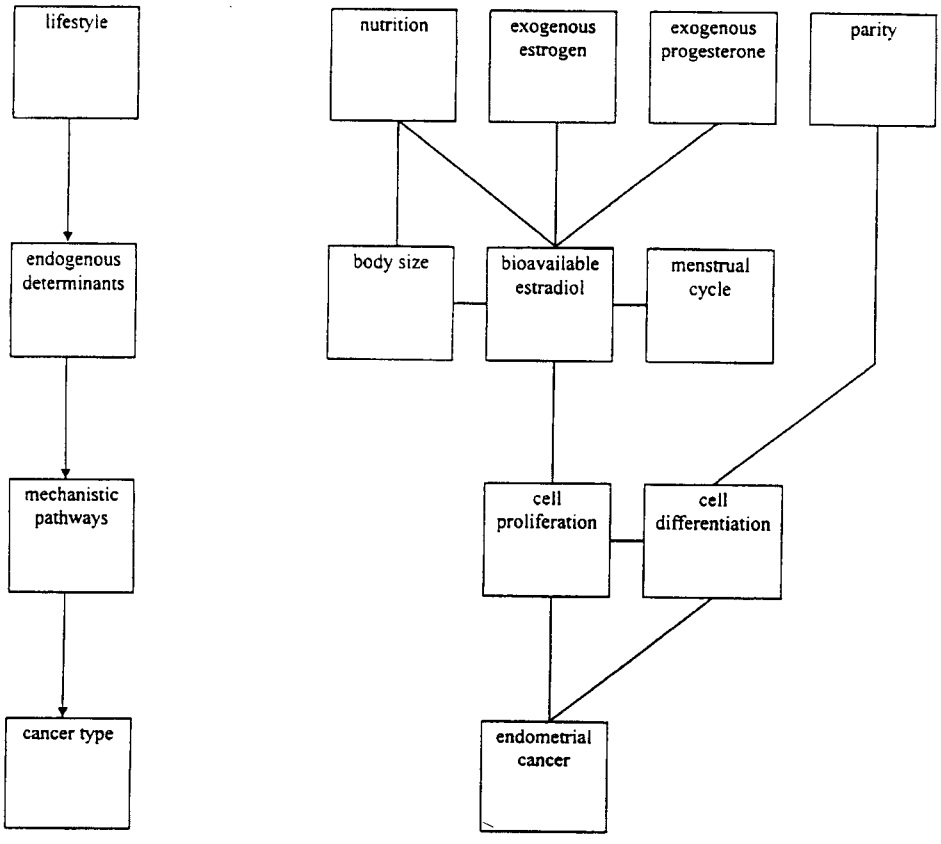

Figure 3.3.2. Mechanistic interrelationship between major lifestyle determinants of endometrial cancer

Estradiol exposure is highly involved in endometrial cancer etiology. Estrogens unopposed by progestagens promote cell proliferation in the endometrium. Menstrual cycle characteristics influence bioavailable estrogen levels. Fat consumption and exogenous estrogen from contraceptives and postmenopause therapeutics increase estrogen levels, whereas exogenous progesterone decreases estradiol levels. Parity decreases risk possibly by induction of maturation and full cell differentiation in the endometrium once it becomes functional through pregnancy.

3.4 Cervical Cancer

3.4.1 Epidemiology

Cervical cancer is the second most common cancer in women and, despite the low fatality rates, an important health problem worldwide. Incidence rates are generally higher in economically

developing countries, particularly in Columbia, Mexico, Eastern Europe and parts of India and Asia (figure 3.4.1. c). In the developed world, incidence and mortality have been reduced as a consequence of prevention and screening programs, respectively. Dutch incidence rates are stable around 7 in 100.000 women (figure 3.4.1. a) (NCR). Cervical cancer incidence is higher in blacks compared to whites and is still higher among Hispanics and Native Americans. Asian-Americans have rates similar to those of whites. Incidence is not age-specific. After the age of 20, incidence rapidly increases and readily plateaus (figure 3.4.1. b).

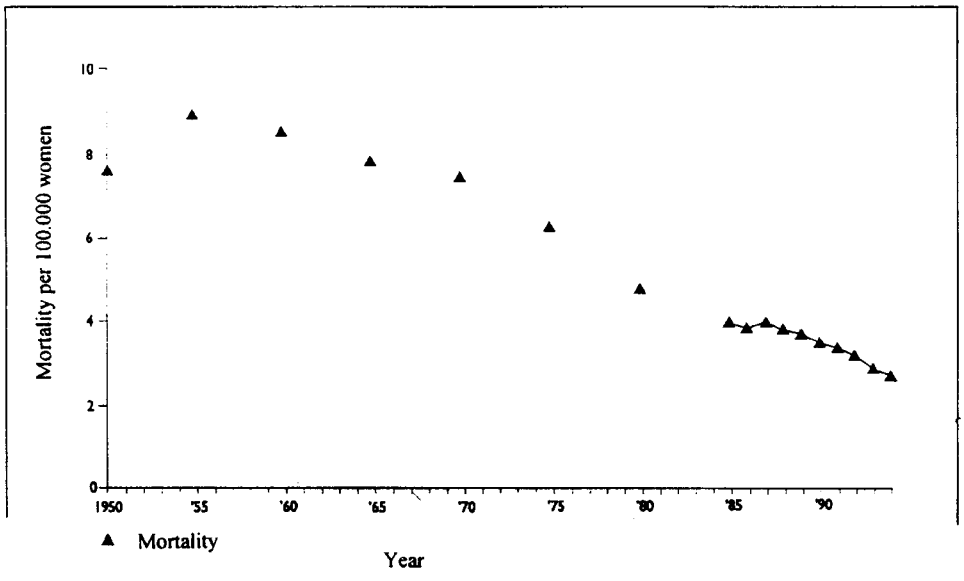

Figure 3.4.1. a: Cervical cancer mortality in The Netherlands (SRK)

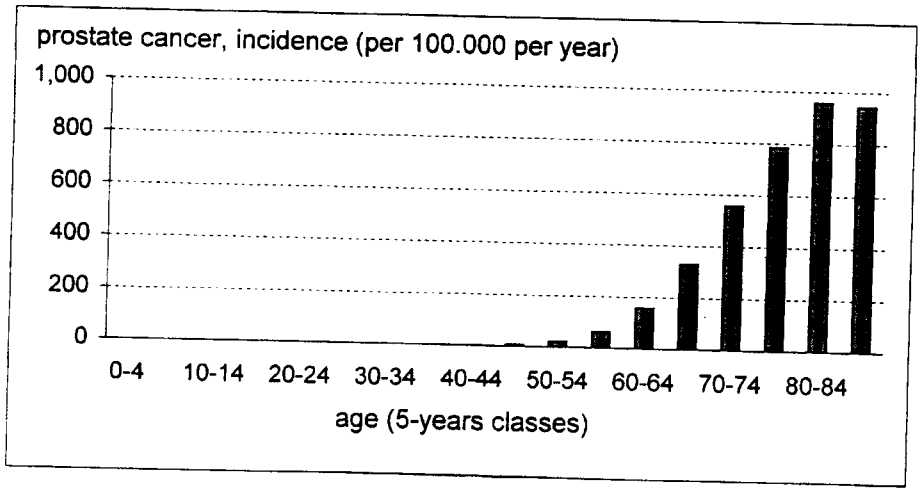

Figure 3.4.1. b: Age specific cervical cancer incidence in The Netherlands (VTV)

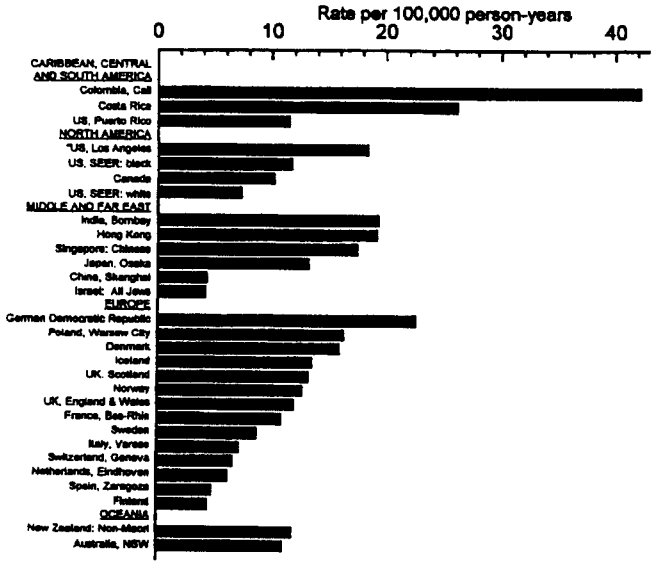

Figure 3.4.1. c: Cervical cancer incidence by area (CEP)

3.4.2. Determinants

Human Papilloma Virus (HPV) infection is considered as the major cause of cervical cancer. Since cervical infection with HPV is common compared to the relatively rare development of cervical cancer, additional factors must be involved. HPV infection, however, is the necessary condition. Other established cervical cancer determinants include sexual behaviour and parity.

Infectious agents

- Human Papilloma Virus Infection

A remarkably strong and consistent association between HPV infection and cervical cancer exists (CEP; FNPC; Herrero, 1996; Morris et al, 1996; Nonnenmacher et al, 1995; COMA). Odds ratios of 9 to 167 have been found (Hernandez-Avila et al, 1997). Nearly all women with cervical cancer have detectable HPV DNA, compared to a remarkably lower percentage in controls (CEP; Hernandez-Avila et al, 1997) and almost all cervical tumors contain HPV DNA (CEP; FNPC). Animal and experimental studies as well as cellular and molecular biological data strongly support the evidence that HPV infection is the main cause of cervical cancer (CEP). HPV causes growth abnormalities and transforms human cell lines in vitro (CEP). Over 70 types of HPV have been identified. HPV 16 is the most important cancer-associated type, along with HPV types 18, 31 and 45 (CEP; Hernandez-Avila et al, 1997). Since HPV infection of the cervix is common, other factors, like intensity of infection, immunologic response and/or genetic predisposition of the host, as well as lifestyle determinants, must be involved in the etiology of cervical cancer (CEP). Genital HPV infections are transmitted easily (CEP). In the future, HPV immunization of the general population may prevent development of cervical carcinoma.

- Other infectious agents
Infection with Herpes Simplex Virus 2, Chlamydia or additional microorganisms are possibly not related to cervical cancer risk, since no association remained after adjusting for HPV infection (CEP). It has been suggested that either HPV infection or cervical cancer suppresses the immune system resulting in an increased susceptibility for infectious agents. In addition, microorganism infection is associated with sexual activity and HPV infection (CEP).

Sexual behaviour

Cervical cancer risk is inversely correlated with age of first sexual intercourse (CEP; Biswas et al, 1997; Bosch et al, 1997; COMA). Early first intercourse (below age 16) increases risk two to tenfold compared to first intercourse at age 20 or above (CEP; Biswas et al, 1997). The association remains after adjusting for the number of partners
Cervical cancer risk increases directly with the number of sexual partners (CEP; Biswas et al, 1997; COMA). After adjustment for HPV infection, the associations between age at first intercourse and number of partners and cervical cancer risk are weakened but still apparent (CEP).
Characteristics of the male sexual partner are important cervical cancer determinants. Elevated rates of cervical cancer among the wives of men with penile cancer and geographic clusters of cervical and penile cancers have been reported (CEP). In addition, cervical cancer risk increases with the number of sexual partners of the male partner and depends on history of genital diseases transmitted by microorganisms, visits to prostitutes and poor hygiene of the male partner (CEP).
Use of barrier methods of contraception (condom or diaphragm) is inversely correlated to cervical cancer (CEP). The protective effect can be attributed to the fact that condoms and diaphragms protect the cervix from venereally transmitted microorganisms such as HPV.

Reproduction

Multiparity is associated with increased cervical cancer risk. After adjustment for separate effects of reproduction, sexual activity and HPV infection, the increased risk remains (CEP). It has been proposed that parturition causes cervical trauma, resulting in an increased susceptibility (CEP). In addition, the increased risk of multiparity may be attributable to effects of nutritional status during pregnancy (CEP).

Hormonal exposure

- Oral contraceptive use
Long-term oral contraceptive use is associated with increased cervical cancer risk (FNPC; CEP; LaVecchia 1996). Studies examining this association are, however, difficult to interpret due to the confounding effects of sexual and screening behaviour (CEP).
- DES exposure
Prenatal DES exposure increases the risk of clear-cell adenocarcinoma of the vagina and cervix (Hatch 1998, Boyd 1996, CEP). Cervical cancer occurs at the squamocolumnar junction at the mouth of the cervix, where two types of epithelium join. After birth, changes occur in the distribution of both types of epithelium, called squamous metaplasia. This area has a unique sensitivity for neoplastic events. DES-exposed daughters have an increased area of squamous metaplasia, which explains their increased chance for developing cervical neoplasia (Robboy ea 1984, CEP).

Nutrition

To date, no convincing association has been found between nutritional factors and cervical cancer risk (CEP; FNPC; COMA). None of the studies available adjusted for HPV infection (CEP; COMA). Although vitamin A analogues are dermatologically used in the treatment of warts (which are caused by HPVs), dietary vitamin A intake is probably not associated with cervical cancer risk (CEP). Carotenoids and vitamin C and E may be protective, which may be due to stimulation of cell differentiation and antioxidant defense respectively, but more research is required (CEP; FNPC; COMA). Theoretically, folate deficiency may increase cervical cancer risk due to a suppressed immune system and/or increased DNA damage (FNPC). It has been hypothesized that folate deficiency, which occurs during pregnancy, may be an explanation for the increased risk of multiparity (CEP). However, epidemiologic studies (case-control and cohort) generally show no association between folate status and cervical cancer risk (CEP; FNPC; COMA).

Exposures

- Cigarette smoking
The association between cigarette smoking and cervical cancer risk is unclear. Many studies reported an increased risk (CEP; FNPC; COMA). However, a strong correlation between smoking and sexual activity and low socioeconomic status exists in many countries. Indeed, after adjustment for HPV status, no significant association was found (CEP; Phillips, Smith, 1994). Theoretically, the immunosuppressive effects of smoking may increase the persistence of HPV (CEP). Smoking-derived compounds, including nicotine, have been detected in the cervical mucus of smokers (CEP; FNPC) but it is not clear whether this presence is involved in cervical cancer etiology.

Environmental chemicals

There is no indication that environmental chemicals, like endocrine disrupting compounds, affect cervical cancer risk (Waddell, 1998).

Other determinants

- Socioeconomic status
Cervical cancer affects women of low socioeconomic status more frequently than women in the upper socioeconomic class (CEP; Herrero, 1996; Bjorge, Kravdal, 1996). However, after adjustment for sexual behaviour and HPV status, the association was considerably reduced. Epidemiologic evidence shows that HPV infection is more prevalent in women of lower educational and income levels (CEP). Therefore, it appears that the increased risk among women of low socioeconomic status is largely attributable to an increased HPV infection risk. Other correlates of lower socioeconomic status, like dietary habits and multiparity could be involved in cervical cancer etiology as well.

3.4.3 Mechanistic Summary

Cervical cancer occurs in squamous metaplastic cells at the mouth of the cervix, where two types of epithelium join. Lifestyle determinants of cervical cancer are summarized in figure 3.4.2.

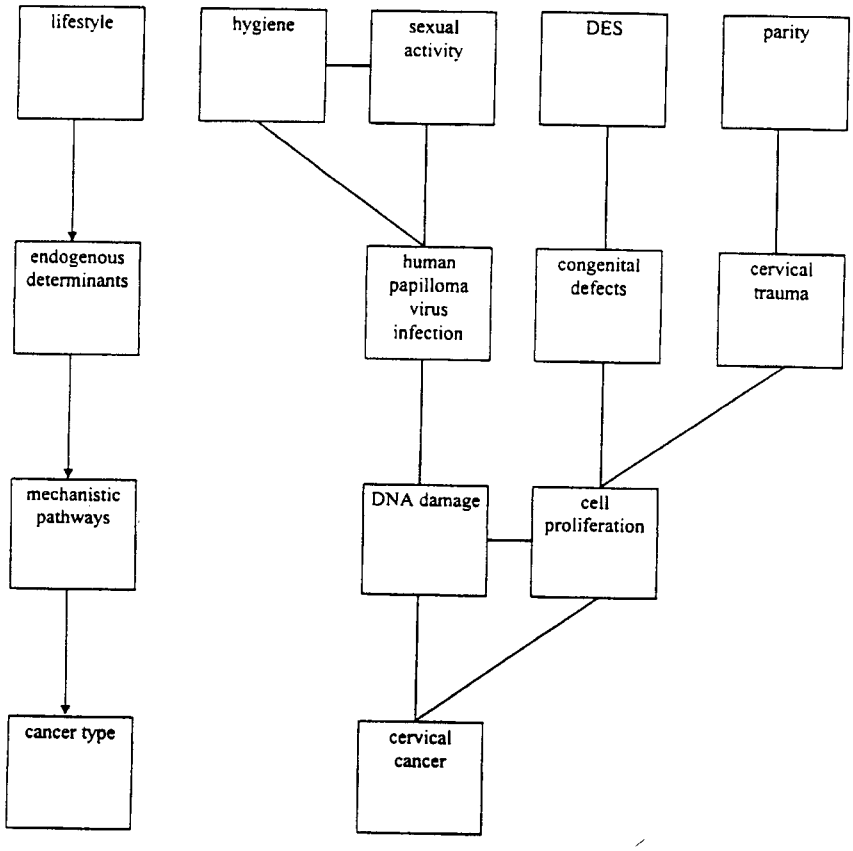

Figure 3.4.2. Mechanistic interrelationship between major lifestyle determinants of cervical cancer

Infection with Human Papilloma Virus (HPV) is the major cause of cervical cancer. Infection chance and degree are influenced by lifestyle factors such as personal hygiene and sexual behaviour. HPV-infection may lead to DNA-damage and neoplastic transformation.
Prenatal DES-exposure leads to congenital increases in the area of squamous metaplasia and thereby increases cervical cancer risk.
On the other hand, cervical trauma, which increases with parity through repeated extreme stretching of the cervix, may cause tissue repair mechanisms to stimulate local cell proliferation.

3.5 Testicular Cancer

3.5.1 Epidemiology

Throughout the world, incidence rates of testicular cancer are increasing. The overall age-adjusted incidence rate of testis cancer has increased 3.5-fold in Connecticut during the past nearly 60 years of cancer registration (Zheng et al, 1996). Mortality rates of cancer of the testis are declining,

because of advanced testis cancer treatment. Cancer of the testis is relatively uncommon (it affects 2-3 men per every 100,000 in the United States (Kelty et al, 1996)) and it is mostly diagnosed between the ages of 20 and 44 years (figure 3.5.1. b). The Dutch incidence rates are similar to those in the US, but an increase has not been observed in The Netherlands (figure 3.5.1. a) (NCR). This may be due to the relatively short period of registration (since 1989).
During the period between 1973 and 1990, age-adjusted testicular cancer incidences in the United States increased with 60% in whites but decreased with 16% in blacks; concurrently, age -adjusted mortality declined with 65% in whites and with 37% in blacks.
The age-adjusted incidence among whites in 1986-1990 was about seven times that among blacks in the United States.
Even though the age-adjusted incidence of testicular cancer is relatively low in all populations of the world, there is considerable geographic variation (figure 3.5.1. c) (CEP).

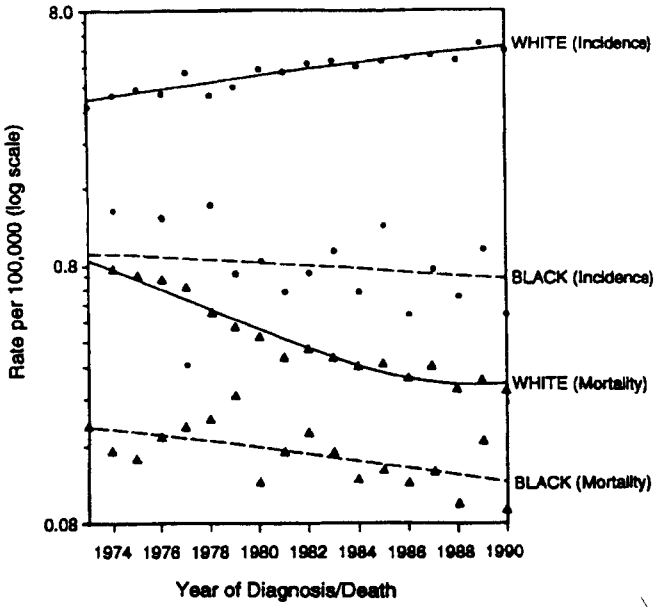

Figure 3.5.1. a: Testis cancer incidence and mortality in the USA (CEP)

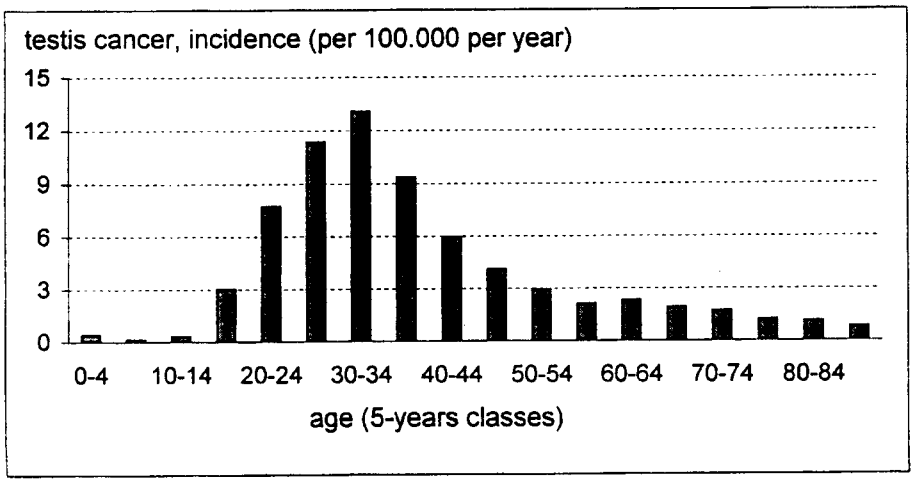

Figure 3.5.1. b: Age specific testis cancer incidence in The Netherlands (VTV)

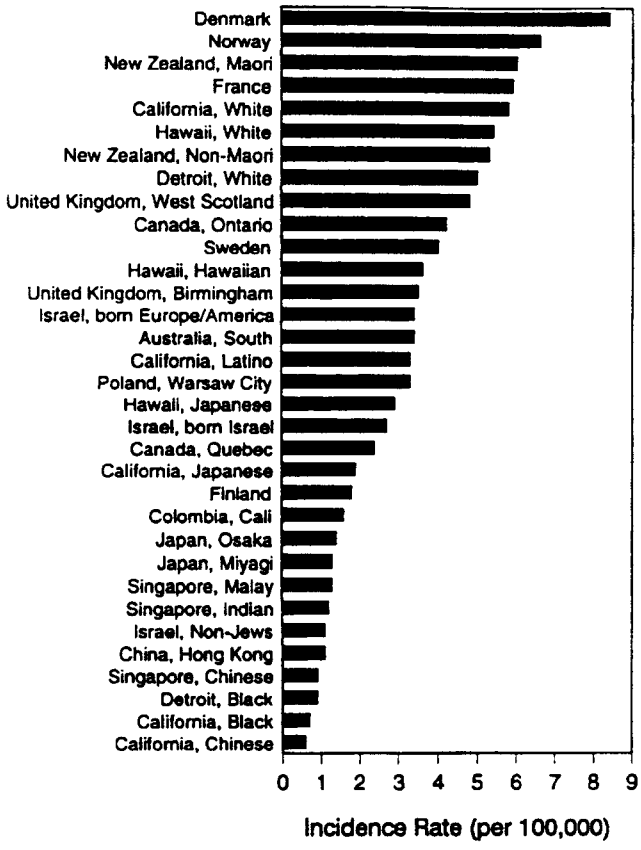

Figure 3.5.1. c: Testis cancer incidence by area (CEP)

3.5.2 Determinants

The exact etiology of testicular cancer is unclear, although several lifestyle factors seem to be important.

Sex hormone exposure

DES exposure in utero has been linked to a variety of structural and functional alterations in the human male genital tract (CEP). Prenatal estrogen exposure is a possible risk factor for testicular cancer in men (Bosland, 1996). Pregnant mice treated with ethinyl oestradiol produced offspring who were significantly more likely to have a cryptorchid testis and who had an increased risk, although not statistically significant, of a testicular teratoma (Walker et al, 1990).
The case-control studies that investigated the correlation between exogenous estrogen use and testicular cancer risk observed inconsistent results. However, animal studies reported that exposure to exogenous estrogens during fetal development will profoundly alter sexual differentiation (CEP). In the fetus, unconjugated estrogen can bind to target organ receptor sites in the male genital tract with resultant antagonistic or inhibitory effects on the pituitary-gonadal axis, and on the normal production and distribution of testosterone from the fetal testis (CEP).
Epidemiological and clinical data indicate a common etiology between testicular germ cell cancer and other abnormalities in male reproductive health (such as infertility and cryptorchidism) (Petersen et al, 1998). These observations are in agreement with the suggestions of hormonal involvement in the etiology of testicular cancer.

The presence of androgen receptor protein immunoreactivity in neoplastic germ cells suggests that androgens may be involved in the pathogenesis of testis cancer (Rajpert-De Meyts et al, 1992).

Nutrition

- Milk and dairy products
Testicular cancer patients consumed significanctly more milk in adolescence than population controls, but this difference did not apply to other dairy products or fruit. For each quarter pint of milk consumed the odds ratio was 1.39 (Davies et al, 1996). However, the estimation of milk intake in this study may have been biased.
- Phytoestrogens
Phytoestrogens had no adverse effects on the reproductive system in rhesus monkeys, as evaluated by reproductive hormone concentrations and organ weights at necropsy (Anthony et al, 1996).
Physical activity

A moderate to high level of recreational activity was associated inversely with testicular cancer risk (OR = 0.6) (Gallagher et al, 1995).There was a significant association with sedentary lifestyle and a moderate protective effect of exercise for testis cancer risk (BMJ, 1994). Low amounts of exercise may be related to effects of exposure to endogenous hormones.

Congenital defects

- Cryptorchidism
Case-control and cohort studies have found a positive association between testicular cancer in men and undescended testis. They also reported that cryptorchidism accounted for approximately 10% of the incident cases of testicular cancer. Studies of the incidence of cryptorchidism in England and Wales, comparing the rates in the late 1950s with those in the mid-1980s, have concluded that there has been an increase of 65%-100% (CEP). Cryptorchidism is a consistent risk factor for testicular cancer in men (Bosland, 1996; Davies et al, 1996). There was a significant association of testicular cancer with undescended testis and inguinal hernia (BMJ, 1994; Gallagher et al, 1995; Prener et al, 1996). Cryptorchidism damages the tubular epithelium in mice (Valencia et al, 1996).
Risk was significantly elevated in testis that had had biopsy samples removed during orchidopexy (RR = 66.7) and was significantly greater in these testis than in undescended testis that had not had biopsy samples taken at orchidopexy (RR = 6.7) (Swerdlow et al, 1997).
It was inferred that surgical correction of unilateral cryptorchidism before the age of 10 years was an effective preventive intervention for testicular cancer in young men (BMJ, 1994). The potential reversibility in risk with early surgical correction, and limited risk to the contralateral testis in unilateral cryptorchism, would argue in support of the hypothesis that the microenvironment (e.g. temperature) of the undescended testis is a determining pathogenic factor.
There is no increase of carcinoma in situ of the testis in moderately oligozoospermic men (Giwercman et al, 1997).

Ethnic background

The age-adjusted incidence of testicular cancer in whites in 1986-1990 was about seven times that in blacks in the United States. The morbidity rate of testicular cancer in Finland, which has an ethnic background different from that of other Nordic countries, is far lower than Denmark, although the economic, social and cultural conditions are rather similar. Likewise, the morbidity rate of testicular cancer is many times less than among blacks in both the United States and Africa than

in the white population in the United States. There was a threefold excess risk of cryptorchidism in U.S. whites compared with blacks (CEP).

Exposures

Increased incidences of testicular cancer have been reported in association with employment in a variety of heavy industry (CEP). Men working in these industries have a higher chance of exposure to chemicals such as dyes, oils and metals, which may be related to testicular cancer.

Endocrine disrupting chemicals

It has been speculated that alteration in exposure to estrogenic and other endocrine disrupting agents in the past half-century may have caused the changes in male reproductive health (Jensen et al, 1995). In addition to occupational exposures, environmental estrogens may have played a role in the incidences of testicular cancer and cryptorchidism in men (Sonnenschein et al, 1995). The increase in the incidence of testicular cancer is inconsistent with exposure to PCBs and DDT, since increases in testicular cancer began before use of PCBs and DDT (Waddell, 1998). Until now no direct association between testicular cancer incidence and endocrine disrupting chemicals have been found.

Other determinants

- Socioeconomic status / sedentary lifestyle
Most studies have shown that the incidence of testicular cancer is highest in the professional and skilled nonmanual occupations and that the rates are approximately double the incidence in blue collar occupational groups (unskilled and partly skilled occupations). Such observations do not readily suggest a specific occupational exposure, but may serve to indicate that other risk factors correlated with socioeconomic status and lifestyle (e.g. a sedentary lifestyle) are intrinsically linked in the causal pathway (CEP).
- Testicular trauma
Patients with testicular cancer may recall a history of trauma to the affected testicle (CEP). However, the assessment of risk in case-control studies may be biased by selective recall of instances of trauma of ill-defined severity, or where the trauma called attention to the existing tumor.
- HIV infectionInitial observations of the occurrence of testicular cancer in men with HIV infection resulted in hypothesizing that the infectious agent was a possible causal factor. Recent epidemiologic studies have failed to establish an association (CEP).
- Vasectomy
Following vasectomy, morphologic changes in the human testis have been observed and it is hypothesized that this could lead to testis cancer. However, in case-control and cohort studies their is either no or a weak association found between vasectomy and testicular cancer (CEP; BMJ,1994; Moller et al, 1994).
- Testicular temperature
An increase in local temperature is positively associated with testicular cancer. The temperature of the testicles is higher in cryptorchid men and these men also have an elevated risk for testicular cancer (CEP). Heat may be one of the most important cofactors for the association between a sedentary lifestyle and rising incidence of testis cancer (Oliver et al, 1997). Occupational exposure to extreme low and high temperatures may increase the risk of testicular cancer independent of other

potential risk factors (Zhang et al, 1995). An animal study suggests that hyperthermia damages the tubular epithelium of the testicles (Valencia et al, 1996).
- Height
Risk of testicular cancer increased with height, with subjects taller than 180 cm having a significantly increased risk compared with those 174 cm or less (OR = 1.5) (Gallagher et al, 1995).
- Early age at puberty
Early age at puberty is associated with an increased risk for testicular cancer (BMJ 1994). This association may be related to effects of exposure to endogenous hormones.
- Prenatal cigarette smoke exposure
Smoking during pregnancy is suggested as a cause of the increasing incidence rates of testis cancer in Denmark (Clemmesen, 1997). The relatively high incidence of testicular cancer in Denmark coincide with the high incidence of maternal smoking during pregnancy. McBride et al. (1991) had noted the same association in an earlier study. More research will be needed to verify these findings.

3.5.3 Mechanistic Summary

Testicular cancer arises in most cases from germinal cells, in which meiosis, cell proliferation and cell differentiation are carefully regulated by the microenvironment. The most important determinants of testicular cancer known are brought together in figure 3.5.2. High temperature may cause DNA-damage. Testicular physiology is affected by hormone homeostasis, testicular temperature and congenital malformations. These three determinants are closely interrelated and influence proliferation and differentiation of spermatogonia in the germinal epithelium. A series of lifestyle factors modulate the endogenous determinants. Physical activity probably decreases testicular temperature, whereas sedentary lifestyle and body length both have the opposite effect. Increased body length is thought to increase blood circulation in the testis, and in addition body length has been shown to be a risk factor for varicocele (de Waal et al., 1995). The resulting increased circulation increases testicular temperature. Exogenous hormones (DES) and maternal smoking may disturb prenatal development of the testis leading to congenital defects. Exogenous hormones may also interfere with normal functioning of the pituitary-gonadal axis.

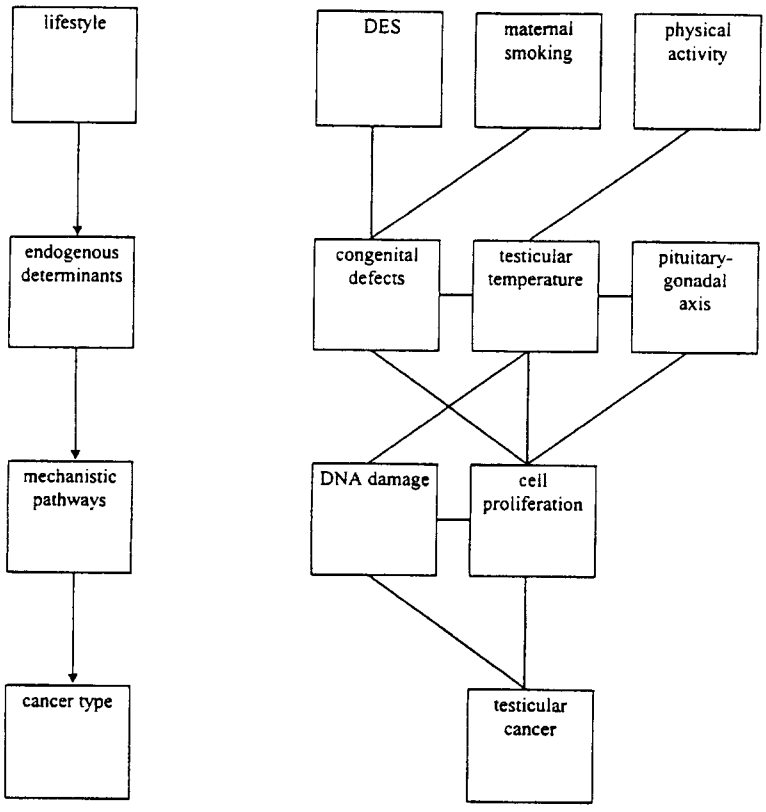

Figure 3.5.2. Mechanistic interrelationship of major lifestyle determinants of testicular cancer

3.6 Prostate Cancer

3.6.1 Epidemiology

The incidence and mortality rates of prostate cancer are increasing throughout the world (FNPC; VTV). It is the ninth most common cancer in the world and the fourth most common cancer in the world in men, with 400.000 cases in 1996 (WHO, 1997).
The incidence and mortality rates vary widely througout the world and are strongly associated geographically (figure 3.6.1. c). The highest rates are found in Europe, North America and Australia. Dutch incidence rate is increasing to around 40 per 100.000 men (figure 3.6.1. a) (NCR). The rates are much higher in economically developed countries. This difference in incidence might be due to improved screening and diagnosis in developed countries, which would increase the discovery rate of latent carcinomas.
Prostate cancer is rare in men under 50 years of age, but its incidence increases almost exponentially beyond that age (figure 3.6.1. b) (FNPC).

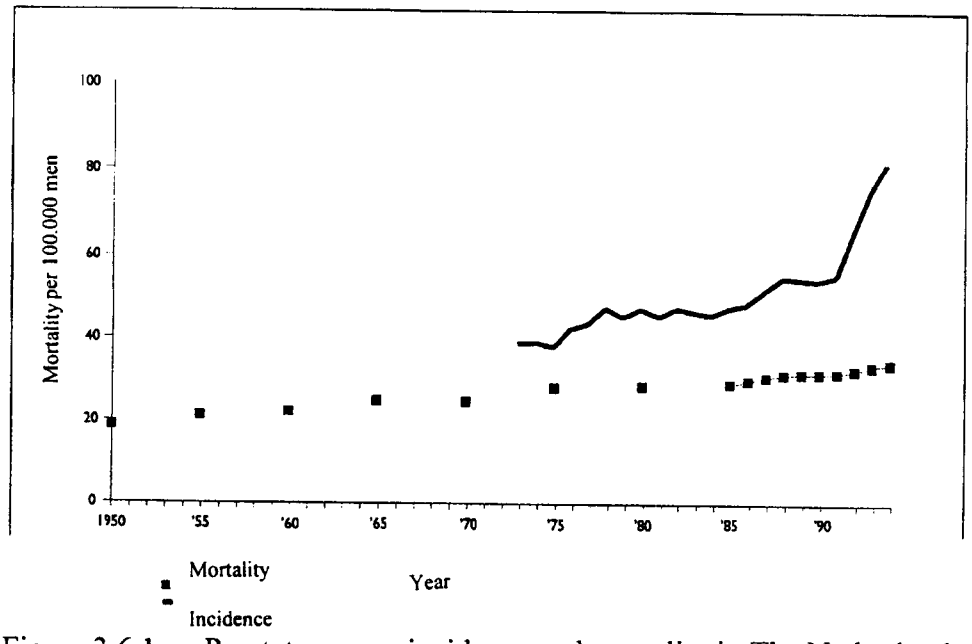

Figure 3.6.1. a: Prostate cancer incidence and mortality in The Netherlands (SRK)

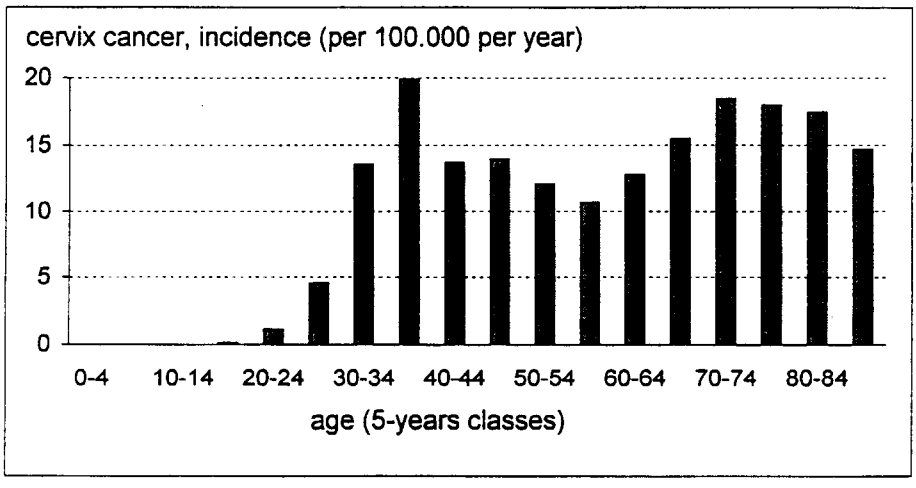

Figure 3.6.1. b: Age specific prostate cancer incidence in The Netherlands (VTV)

Figure 3.6.1. c: Prostate cancer mortality by area (VTV)

3.6.2 Determinants

Many lifestyle and endogenous determinants have been linked to prostate cancer. Particularly lifestyle factors such as nutrition and sexual behaviour are established determinants in prostate cancer etiology.

Sex hormone exposure

The growth of many prostate tumours is hormone dependent. An association between testosterone exposure and prostate cancer risk is plausible, because in eunuchs prostate cancer does not occur (VTV). Most studies have shown a positive association between testosterone levels and prostate tumor growth (CEP). Ablation or antagonism of testosterone production, either through estrogen administration, orchiectomy, or treatment with LHRH agonists or antiandrogens, is used to control disseminated prostate cancer (Murphy et al, 1982; Catalona et al, 1994). A positive association was found between testosterone levels and prostate cancer risk in various ethnic groups (Ellis et al, 1992; Ahluwalia et al, 1981). Japanese and Chinese men appear to have relatively low 5-alpha reductase expression, the enzyme which converts testosterone to its bioactive form, dihydrotestosterone (DHT) (Ross et al, 1992). Black women have 50% higher serum levels of testosterone and 40% higher estradiol serum levels during early pregnancy than do white women (Henderson et al, 1988). It seems plausible that these higher steroid hormone levels in utero may contribute to the higher prostate cancer rate for black men. Ripple et al (1997) found that physiologic levels of androgens are capable of increasing oxidative stress in androgen-responsive LNCaP prostate carcinoma cells.
Case-control studies found either evidence of reduced estrogen levels in cases, increased levels in cases or no differences between cases and controls (CEP).
There are few relevant human data on the possible role of prolactin in prostate cancer etiology and those that exist do not suggest an important relationship (CEP).

Nutrition

-Energy, fat and meat intake
Prostate cancer is possibly associated with caloric intake and fat consumption (FNPC, CEP, COMA). A positive association between energy intake and prostate cancer risk was evident in two cohort studies (Ghadirian et al, 1996; Gronberg et al, 1996). In a population-based case-control study, Andersson et al (1996b) found evidence that total energy intake is a risk factor for prostate cancer (526 patients, 536 controls and 5 years of folluw-up). However, it is difficult to determine whether any increased risk of prostate cancer with high energy intake results solely from caloric intake itself, or from the high intake of dietary constituents or particular energy-dense foods. Epidemiologic data (case-control and cohort studies) generally support a positive association between dietary fat and prostate cancer risk (CEP; FNPC). Most studies reported positive associations between total fat intake, specific high-fat content foods, animal fat, saturated fat and α-linolenic acid on the one hand and prostate cancer incidence on the other. A negative correlation between linoleic acid and the risk of prostate cancer has been reported in three studies (Kaul et al, 1987; Giovannucci et al, 1993; Gann et al, 1994). No associations were found between poly- and monounsaturated fat and cholesterol and the risk for prostate cancer. In a review, Key et al (1995) reported evidence that dietary fat and / or meat may increase the risk for prostate cancer. A statistically significant positive association of prostate cancer risk and total fat intake was found for all ethnic groups combined (Whittemore et al, 1995b). This association was attributable to energy from saturated fats; after adjusting for saturated fat, risk was only weakly associated with monounsaturated fat.
Meat consumption is possibly associated with prostate tumor growth (FNPC; Giovannucci et al, 1996; COMA). Most studies found a moderately increased risk for prostate cancer with high meat consumption. Three cohort studies showed no association, but these studies were of Japanese men or Seventh-day Adventist men. In these populations, meat intake is substantially below that seen among the general population in North America and northern Europe.
In a review Kolonel et al (1996) observed no particular fat component that has been consistently implicated for prostate cancer risk. A notable finding is a strong positive association with intake of animal products, especially red meats, but this in itself does not specifically implicate fat.

-Vitamins
Vitamin A (retinol) has a wide ranging effect on cellular differentiation, growth factor synthesis and immune function. Vitamin A stimulates cell differentiation and inhibits cell proliferation, which can arrest tumor growth. In addition, retinoids have demonstrated effectiveness in inhibiting tumor formation and metastasis in vitro and in vivo (Slawin et al, 1993). The serum studies to date seem to indicate that a higher serum retinol level is associated with a lower risk of prostate cancer. The studies of serum retinol levels, however, are not consistent with the pattern of results from the dietary studies (CEP). Very inconsistent data have been reported about vitamin A in case-control studies.
Provitamin A compounds, such as β-carotene, are able to inactivate free radicals, which are potentially genotoxic. Case-control studies that have evaluated prostate cancer risk in relationship with intake of β-carotene, have found either an inverse association or no association (CEP). Giovannucci et al (1995) showed no relationship between β-carotene and the risk of prostate cancer. They also found that retinol from food sources alone was associated with a moderately elevated risk of prostate cancer in older men, whereas retinol from supplements was not. One prospective study found no relationship between serum β-carotene levels and the development of prostate cancer (Hsing et al, 1990b) and one study reported a decrease in prostate cancer risk with higher serum β-

carotene levels (Knekt et al, 1990). In a cohort, Shibata et al (1992) noted no change in prostate cancer risk with β-carotene consumption.
Vitamin D probably inhibits the growth of prostate cancer cells. This inverse association has been observed by several case-control and prospective studies (CEP). One animal study also noted an inverse relationship. The relative increase in tumor volume was significantly lower (15 %) in the experimental (N = 12) than in the control (N = 12) group of athymic nude mice in the first interval following treatment ($P < 0.01$). (Schwartz et al, 1995). However, in a prospective study Braun et al (1995) showed no statistically significant trends or differences between cases (N = 61) and controls (N = 122) in an analysis of serum level.

-Vegetables, fruit and phytoestrogens
In general, no association has been reported in case-control and cohort studies between vegetables and fruit and prostate cancer risk. In a review, Giles et al (1997) concluded that evidence of a protective effect of fruit and vegetables is weak and inconsistent. Of 46 vegetables and fruits or related products, four (tomato sauce, tomatoes, pizza and strawberries) were significantly associated with lower prostate cancer risk. This suggests a protective action of lycopene (tomato sauce, tomatoes and pizza are primary sources of this carotenoid) (Giovannucci et al, 1995) (47.894 men, four years of folluw-up, 812 new cases). An international study reported a negative correlation between vegetable-derived calories and cancer of the prostate (Rose et al, 1986). In this study, the 1978-1979 mortality rates for prostate cancer in several countries were related to the average 1979-1981 food availibility data published by the United Nations.
Variable results have been reported on the association between phytoestrogens intake and prostate cancer risk. Two studies reported that a soy diet reduces mortality due to prostate cancer (Kao et al, 1995; Adlercreutz et al, 1993) and one study observed an increase in risk with increased consumption of tofu (Severson et al, 1989a).

-Various nutrients
Only three cohort studies have examined egg intake and the risk of prostate cancer. One study found a suggestive positive association between fatal prostate cancer and the consumption of eggs (Snowdon et al, 1984). The other two studies reported no substantial association (Mills et al, 1989; Hsing et al, 1990a).
In general, cohort studies found no association between milk consumption and prostate cancer risk. However, an increased risk was reported with increased butter consumption, which may be attributed to the fat content. Case-control studies noted a positive relationship with more frequent milk consumption (FNPC).
Almost all studies that have examined the relationship between alcohol intake and the risk of prostate cancer were consistent with little or no increase in risk (FNPC; CEP). However, in a review, Hirayama et al (1992) reported an association for men who were daily drinkers. In a population-based case-control study, Hayes et al (1996) reported an increased risk of prostate cancer in U.S. white and black men with alcohol use in excess of 22 drinks per week, and unconfounded by tabacco use.

Body size

- Weight
Most case-control and cohort studies have reported an increased risk for prostate cancer with increased body size (FNPC; CEP). One cohort study reported that higher lean body mass (as assessed by mid-upper arm circumference) was more strongly associated with increased prostate cancer risk than BMI (Severson et al, 1988). In a prospective study, greater body mass index (RR =

1.7 for BMI > 27.8 kg / m2 compared with < 23.6) was an independent predictor of prostate cancer (Cerhan et al, 1997). Andersson et al (1997) performed a large, retrospective cohort study to evaluate a possible association of BMI with the incidence and mortality rate of prostate cancer. A total of 2368 incident cases and 708 deaths from prostate cancer occurred during a follow-up period averaging 18 years. The excess risk of death from prostate cancer was statistically significant in all BMI categories above the reference category (RR = 1.4). Giovannucci et al (1997b) found that the preadult hormonal milieu, as reflected in attained height (positive association) and childhood obesity (negative association), may have a strong influence on prostate carcinogenesis.
- Height
One case-control study reported that height was associated with a moderately increased risk of prostate cancer (Le Marchand et al, 1994) and one cohort study (Andersson et al, 1997) reported that the excess risk in the highest (> 180 cm) compared with the lowest (< 172 cm) categories was positively associated (RR = 1.28).

Physical activity

Several cohort studies that have investigated the relationship between physical activity and prostate cancer risk have found inconsistent results (FNPC; CEP).
As a result of the long latency period for prostate cancer, it is not clear at what point in life physical activity may be most relevant. Some studies that showed a protective association were based on activity in later life (Lee et al, 1992; Severson et al., 1989b), whereas one that showed an increased risk assessed physical activity in young adulthood (Polednak, 1976). Most case-control studies have found that higher levels of physical activity protect against prostate cancer, but the results have not been consistent for all ages and ethnic groups (FNPC).

Exposures

Studies on the association between tobacco use and prostate cancer risk have given variable results (CEP; Cerhan et al, 1997; Coughlin et al, 1996; Hiatt et al, 1994). On the basis of 20 studies, Key (1995) calculated a summary risk ratio very close to one. Most studies found that cadmium exposure, based on dietary, occupational and smoking exposure, was positively associated with prostate cancer. However, they reported no association with dietary exposure alone (FNPC; CEP).

Endocrine disrupting chemicals

It has been proposed that humans have suffered adverse effects on reproductive health as a result of environmental exposure to chemicals that interact with the endocrine system. However, until now no direct association between endocrine disrupting chemicals and prostate cancer risk has been found (Waddell, 1998).

Sexual behaviour

A number of investigators have found evidence that factors associated with increased sexual activity (e.g. early first intercourse, a large number of sexual partners, more frequent sexual intercourse) are associated with increased prostate cancer risk (CEP; VTV; Key et al, 1995; Andersson et al, 1996a). A fairly consistent finding among a large series of epidemiologic studies has been a higher prevalence of past venereal disease among prostate cancer cases than among controls (CEP). Since these types of sexual activity risk factors are similar to those observed for cervix cancer, it has been hypothesized that prostate cancer might be caused by an infectious agent, possibly spread through

sexual activity. An alternative explanation for the association between these indices of high levels of sexual activity and risk of prostate cancer is that they are indicators of circulating androgens.

Ethnic background

Worldwide, there are great differences between incidence rates for prostate cancer (CEP; FNPC; VTV; Imai et al, 1996; Whittemore et al, 1995a). Within countries, substantial variations in incidence also occur; for example, among different ethnic groups in the U.S.A. The highest incidence rates in the world are reported among African-American men and the lowest among men in China. Rates are much lower in Africa than among African-Americans. Although some of these differences are due to differences in detection strategies for prostate cancer between countries, the results of migrant studies appear to show some real shift in incidence toward rates in the new host country, providing evidence that these international and racial differences in prostate cancer incidence are not based entirely on genetic predisposition (CEP). Large ethnic differences may be due to ethnic variation in endogenous factors, such as androgen metabolism or inherited susceptibility (Shibata et al, 1997).

Other determinants

- Vasectomy
Most studies observed a positive association between vasectomy and prostate cancer risk (CEP). Several studies have shown that risk increases over time following vasectomy (Giovannucci et al., 1993). Nine studies reviewed by Key (Key T, Risk factors for prostate cancer, Cancer Surveys 23: 63-77, 1995) gave a summarized risk ratio of 1.54 (CI 1.34 - 1.77). One study has shown increased bioavailable androgen levels in vasectomy subjects, which may indicate a mechanism for the increased risk observed (Honda et al., 1988 in CEP pag 1196). Although these data are presented as reasonably consistent evidence suggesting an increased risk, further study to exclude bias is suggested.
- Circumcision
Circumcision is probably a reducing risk factor for prostate cancer (CEP), with improved hygiene as the most probable mediating mechanism.
- Diabetes
A prior history of a diagnosis of diabetes was associated with a reduced risk of prostate cancer (Giovannucci et al, 1998; Thompson et al, 1989). This inverse association is compatible with a cancer-promoting role for endogenous testosterone, the level of which is lower in diabetes, or a risk-reducing effect of antidiabetic diet or drug therapy.

3.6.3 Mechanistic Summary

Prostate tumours are adenocarcinomas arising in the glandular acini of the prostate. The determinants of prostate cancer are summarized in figure 3.6.2. On the DNA level, a remarkable analogy with cervical cancer as regards the association with sexual behaviour suggests that infections may play a role. Cellular proliferation as a mechanism of prostate cancer development probably relates to the endogenous testosterone level, which is the best established determinant for this type of cancer. Besides, also energy status and body size are correlated with testosterone level. These endogenous determinants are influenced by physical activity and nutritional factors, with fat and meat consumption as positive correlates with prostate cancer. Finally, vasectomy appears to increase the risk for prostate cancer, possibly by interference with androgen homeostasis.

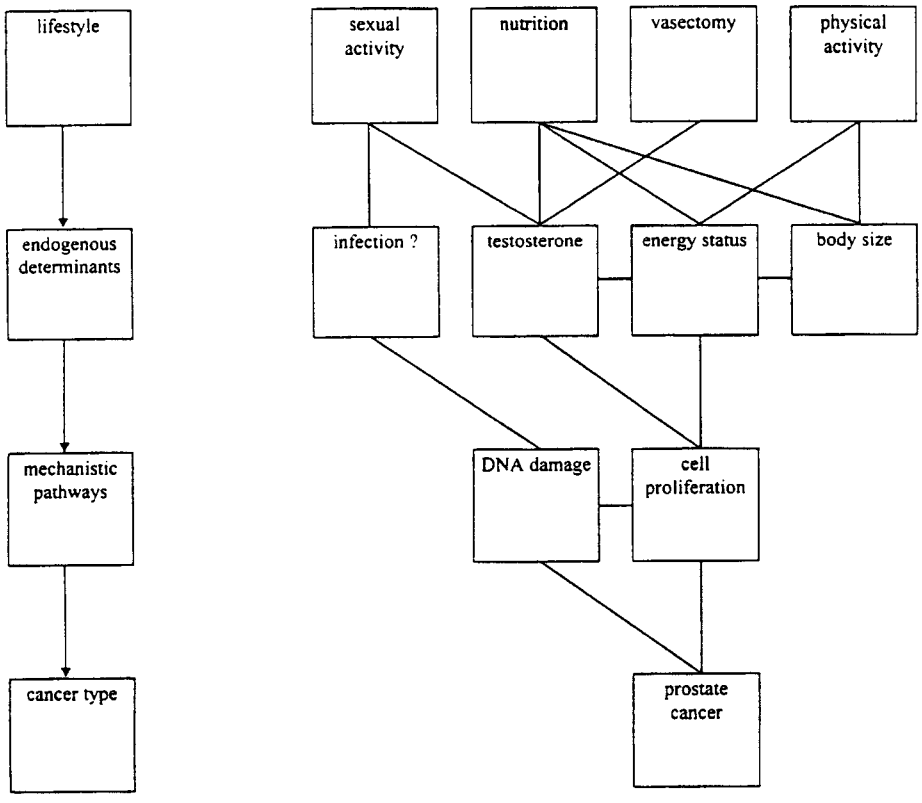

Figure 3.6.2. Mechanistic interrelationship between major lifestyle determinants of prostate cancer

4 Lifestyle and Related Endogenous Determinants

This chapter reviews lifestyle and related endogenous determinants that have been associated with cancer of the reproductive organs. Special attention is given to secular trends as they may correlate with trends in cancer incidences.

4.1 Demography

Life expectancy at birth has been increasing in the past century in the Netherlands. For men, an increase from 70.4 in 1950 to 74.6 years in 1995, and for women from 72.7 in 1950 to 80.4 years in 1995 occurred (CBS). This trend is expected to continue, resulting in life expectancies of 83 years for women and 80 years for men in 2050. Improved medical care, healthier lifestyle, and decreased smoking have been mentioned as causative factors (NIDI, 1997). In conjunction with increased life expectancy the Dutch population has been ageing during the twentieth century. This trend is still ongoing. The percentage of people under 20 years of age decreased from 32.8% in 1976 to 24.3% in 1996, whereas the age group of 65 years and up increased from 12.5% to 13.3% in this time period (CBS) (figure 4.1.a).

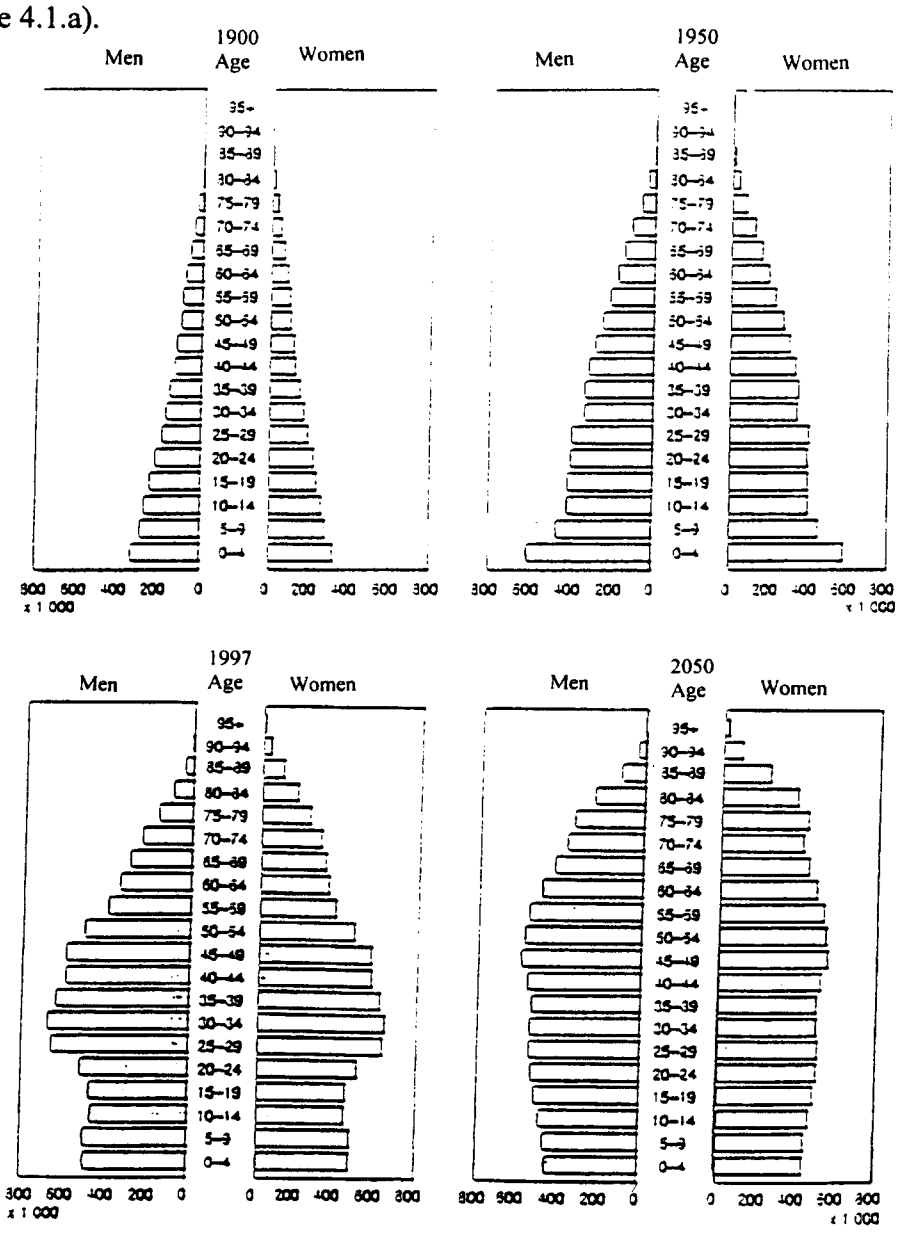

Fig. 4.1.a Age distribution in the Dutch population (CBS)

4.2 Anthropometry

Industrial countries throughout the world show a secular trend towards increased growth rate and adult height of man (Meredith, 1978; Roche, 1979). Similarly, average body length of people aged 20 years and higher in the Netherlands has increased between 1981 and 1996 from 177.2 to 179.4 cm for men and from 165.8 to 167.2 cm for women. Dutch average adult body weights increased from 76.4 to 79.6 kg for men and from 64.9 to 67.1 kg for women in the same period (CBS). The incidence of obesitas, defined as a Body Mass Index (BMI= body weight (kg) / body length $(m)^2$) greater than 30, increased in this period from 5.1% to 6.9% of adults (CBS).

4.3 Food Consumption

Between 1945 and 1980 energy intake (7%) and saturated fat intake (10%) increased in the Netherlands, whereas intake of vegetable protein (30%), carbohydrates (10%) and fiber (10%) decreased. Intake of antioxidant vegetables and fruit decreased and meat has increased between 1965 and 1975. As compared to the Dutch food consumption guidelines ("Richtlijn Goede Voeding"), fat intake is too high (40 versus 30-35 energy%) whereas carbohydrate (43 versus 55 energy%) and fiber intake (2.4 versus 3 gr/MJ) are too low (VTV).

4.4 Stimulants Intake

Alcohol consumption (figure 4.4.a.) has increased dramatically in the Netherlands between 1950 and 1980. Beer consumption increased ninefold and wine consumption even 25-fold in this time period. After 1980 alcohol consumption has tended to stabilize (VTV).
Smoking (figure 4.4.b.) has decreased in the Netherlands in men from 90% of the population in 1958 to 38% in 1992. In women, smoking has increased from 29% in 1958 to 40% in 1975. In both sexes a stabilization has been observed in the last decade (VTV).

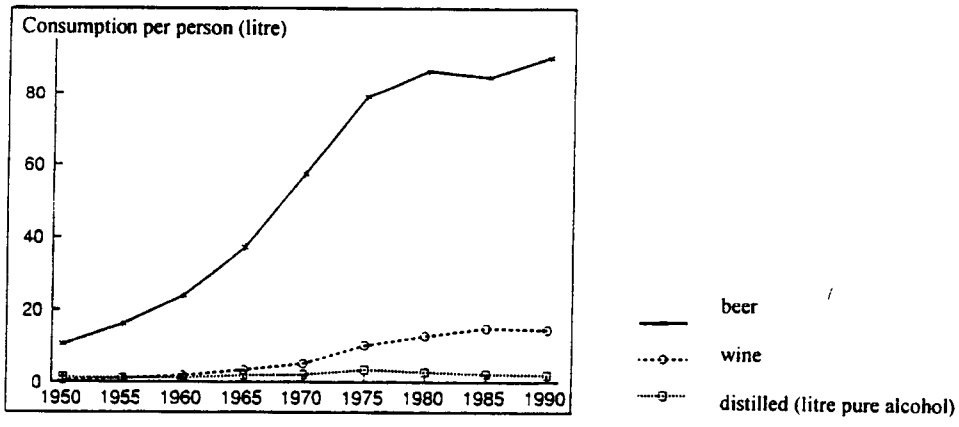

Fig. 4.4.a. Alcoholic beverage consumption in the Netherlands between 1950-1990 (VTV)

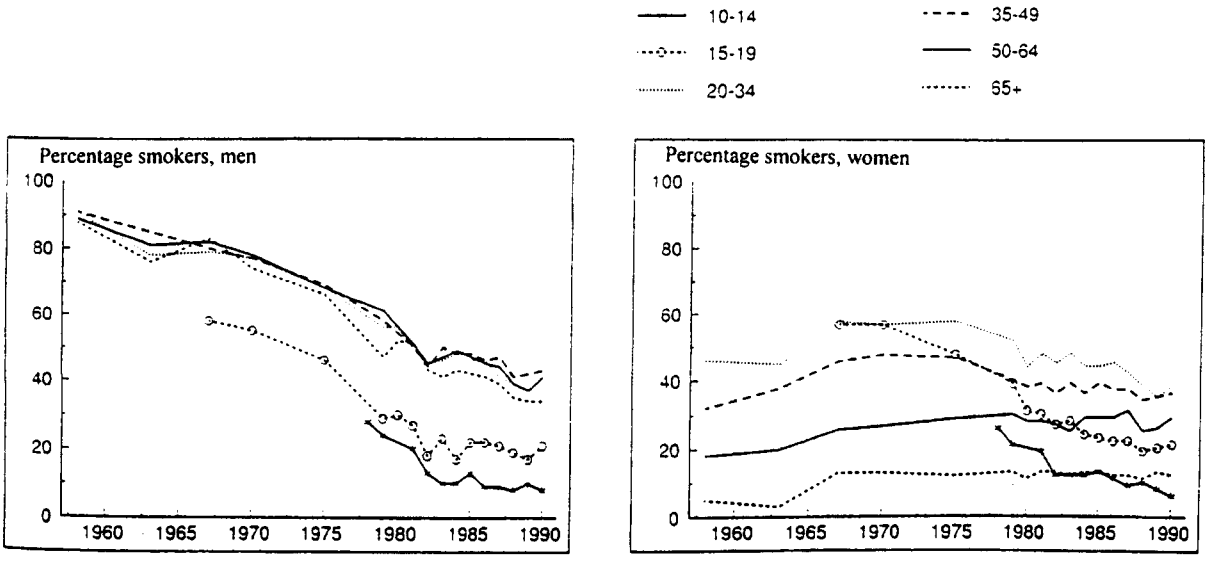

Fig. 4.4.b. Percentages smokers in Dutch age groups 1958-1990.

4.5 Reproductive Behaviour

Under this heading we will consider trends in lifestyle factors relating to reproduction, such as age at first intercourse, number of sexual partners, age at first pregnancy, parity and duration of breastfeeding.

Average age at first intercourse is most likely decreasing in the Dutch population (VTV, 1993). Coital experience in 16 year olds increased from 16% in 1981 to 33% in 1989. In addition the percentage of teenagers who had sex with two or more partners increased from 9% in 1968 to 22% in 1989. On the other hand the establishment of stable partnership is delayed. The increase in divorces has lead to an increase in changing sexual contacts. Taken together, there is a trend towards increased sexual activity both early and later in life.

In The Netherlands, the age at first birth has been increasing since 1970 (NIDI, 1997). This trend is still ongoing, with maternal age at first birth increasing from 26.5 years in 1985 to 28.6 years in 1995 (CBS). The latter number is the highest ever observed in the world (NIDI, 1997).

Parity has shown a decrease from 4.5 in 1900 to around 1.6 in the seventies, followed by a stabilization around the latter number (CBS). A temporary increase in parity occurred in the years after the second world war.

No change is apparent in the duration of breastfeeding. Around 70% of children are breastfed from birth, at three months of age slightly less than 50% is still breastfed, and at 6 months of age the percentage is still close to 30% (CBS). These numbers refer to the period since 1989, before that time no data were found.

4.6 Male Vasectomy

Vasectomy as a method of contraceptive sterilization is widely used in modern society. In 1991, 12% of married men aged 20-39 had had a vasectomy in the USA (Forste et al., 1991). A survey in New Zealand revealed that sterilization had become the most common means of family limitation, with vasectomy as the most common method (Paul et al., 1988). We have found no specific data on secular trends, but a considerable increase over the last 3 to 4 decades seems very likely.

4.7 Sex Hormone Exposure

Exposure to sex hormones may occur through endogenous hormone production in the body, and also through exogenous exposure, mainly via contraceptives and postmenopausal therapy, as detailed below.

4.7.1 Endogenous Estrogen

Estrogen is produced by the ovaries throughout the female fertile period, which is limited in time by menarche and by menopause.
The mean age at menarche has shown a decreasing trend over the last century, as has been reported by studies throughout the world (Oduntan 1976; Cameron, 1979; Roche, 1979; Dacou-Voutetakis et al., 1983; Vercauteren and Susanne, 1985; Tzusaki et al.,1989; Rosenberg, 1991; Veronesi and Gueresi, 1994; Tryggvadottir at al., 1994). A study in The Netherlands has shown the same finding (Venrooy-IJsselmuiden and Smeets, 1976). The absolute decrease observed varies between studies, and amounts on average several months per decade. Since the sixties a leveling-off of menarchal age has been observed by various authors (Veronesi and Gueresi, 1994; Vercauteren and Susanne, 1985; Helm and Grolund, 1998; Tryggvadottir at al., 1994; Dacou-Voutetakis et al., 1983), although recent decreases have also been observed (Loukid et al, 1996). Recent mean menarchal ages are estimated between 12.5 and 13.5 years of age. The trend in menarchal age corresponds with socioeconomic changes and with increasing body size and weight in children (Brundtland et al., 1980; Liestol, 1982; Vercauteren and Susanne, 1985; Rosenberg, 1991). All these factors have shown a discontinuity during the second world war (Liestol, 1982).
A secular trend towards a later age at menopause has been proposed (Flint, 1987). Subsequent studies however have invariably found no changes in age at menopause (McKinlay et al., 1985; Parazzini et al., 1992; McKinlay, 1996). Current mean age at menopause is around 50-51 years of age. Lifestyle factors appeared to have minimal influence in a Dutch study (van Noord et al., 1997). On the other hand, smoking has been repored to decrease age at menopause with at least one year on average, and parity increases age at menopause with half a year on average (McKinlay et al., 1985; Parazzini et al., 1992). Body weight is positively correlated with age at menopause (Hoel et al., 1983).

4.7.2 Exogenous Estrogen

Exposure to exogenous estrogens has occurred mainly through contraceptive treatment and postmenopausal therapy.
Hormone contraceptive use has increased dramatically since the seventies. An average yearly increase with 1.4% in The Netherlands between 1981 and 1995 has resulted in around 45% of women aged 16-49 taking hormone contraceptives (CBS). The increase is relatively largest in the 16-19 age group, with 27% users in 1985 and 49% in 1996.
Postmenopause hormone therapy is used to relieve postmenopausal vasomotor and genitourinary symptoms, and to decrease risk of cardiovascular disease and osteoporosis. This therapy became popular during the sixties and seventies, and in that period estrogens were prescribed without progestagens. Popularity declined after the stimulating effects on endometrial cancer became apparent. Sales increased again after combination therapy of estrogen with progestagens came available, which did not have these detrimental health effects (Carr BR, Eur.J.Obstet. Gynecol. Reprod. Biol. 64 S1: S17-S20, 1996; Hemminki E and Topo P. J.Psychosom. Obstet. Gynecol 18:

145-157, 1997). In 1993, 34% of women aged 40-60 were on postmenopause therapy in a US survey. In 1996, of Finnish women between 45 and 64 years of age, nearly 30% were on postmenopause therapy.
Diethylstilbestrol (DES) is a synthetic estrogen that was used widely in the fourties and fifties to prevent threatened abortion in women. The compound has a low serum protein binding capacity and is as effective as estradiol on the estrogen receptor. DES use was discontinued after congenital malformations in genitalia and an increased risk for cervical cancer in offspring became apparent.

4.7.3 Endogenous Testosterone

Endogenous testosterone exposure occurs from male puberty onward. Early puberty increases lifetime exposure to testosterone. Data on trends in age at male puberty are lacking, but in view of trends in body length and female menarchal age it can be inferred that also for males, the age at the onset puberty is decreasing. In addition, voice break nowadays occurs mostly in 13 and 14 year olds, whereas for instance in the 17th century male sopranos at age 16 and 17 were readily available. There are reports suggesting an association between sexual activity and testosterone level (Tsitouras et al., 1982). There is no consensus however on this subject, and it is unclear whether sexual activity induces increased testosterone levels (Brown et al., 1978).

4.7.4 Environmental Exposures

Colborn et al. (1993) published a list of endocrine disrupters and reproductive toxicants that might be involved in wildlife and human effects on reproduction and reproductive organs. Compounds found in high concentrations in areas where wildlife effects were observed were PCB's and DDT. PCB's were first synthesized in 1929, and the insecticidal properties of DDT were discovered in 1939. Both compounds have been used widely since the nineteenfourties. Dioxins were introduced into the environment even later (Waddell 1998, Rappe 1991). Other anthropogenic compounds in the Colborn list were introduced lateron. Exposure to organochlorine compounds has probably been declining since the nineteensixties (Cuijpers et al., 1997). This is exemplified by the fact that the percent of the population with PCB levels above 1 ppm in the fat has declined from more than 60% in 1972 to 5% in 1983 (Mack and Mohadjer, 1985). Similarly, PBPK models for concentrations of dioxins and furans in Dutch human breast milk predict a decline in organochlorine content of around 20% between 1993 and 1998, which on the basis of the recent decline of concentrations in food is probably an underestimation (Cuijpers et al., 1997). The questions of the extent of human exposure and the endocrine potency of these compounds has not yet been sufficiently answered. Safe (1995) estimated the estrogenicity of xenobiotic compounds on the basis of estrogen receptor binding and expected exposure. He suggested that the estrogenic exposure to organochlorine compounds is at least seven orders of magnitude lower than the exposure to phytoestrogens and endogenous estrogen. Moreover, therapeutic estrogen exposure is one to three orders of magnitude higher than endogenous exposure. Harrison et al. (1995) arrived at a similar conclusion. Although these estimates are reassuring, for most of the alleged endocrine disrupters actual exposure data are not yet available.

5 General Discussion

The twentieth century has seen profound socio-economic changes in western societies. Life expectancy has increased. Nutrition has improved and physical activity has decreased, and as a consequence body size has increased and obesity is more common. Alcohol consumption has increased, and smoking has shown a decline in men and an increase in women. Puberty and the onset of sexual activity occurs at earlier age, sexual activity and number of partners increased, whereas maternal age at first birth increased and parity decreased. The application of exogenous hormones for contraception, infertility treatment and postmenopause therapy has greatly increased. In addition vasectomy as a contraceptive measure has increased.

These lifestyle and related endogenous factors have all been shown to be determinants of cancers of the reproductive organs as summarized in table 5.1. Although other determinants have been described (see earlier chapters), we will focus here on major lifestyle determinants only. For these determinants mechanistic information has been discussed above which suggests a possible causal relationship with reproductive organ cancer. It should be noted that besides lifestyle determinants other changes in society profoundly affect cancer incidence. For instance, increasing life expectancy results in aging of the population, which will increase the prevalence of age-related cancer types such as breast, ovarian, endometrial and prostate cancer. In addition, improvements of screening and diagnostic tools will increase detection of cancers and therefore increase their observed incidence. Prevention programs on the other hand will decrease cancer incidence. Finally, the relative contribution of each of the known determinants to cancer incidence is very hard to estimate. For breast cancer, one of the more extensively studied types of cancer, one third of the incidence has been roughly estimated to be explained by the determinants presently known (VTV). This would imply that the largest part of cancer causes is still unknown.

Table 5.1. Associations between reproductive organ cancer types and major lifestyle determinants*

cancer type	breast	ovary	endometrium	cervix	testis	prostate
current Dutch incidence per 100.000 women or men per year	130	10	10	7	3	40
caloric intake	+		+			+
physical activity	-				-	
alcohol consumption	+					
maternal smoking					+?	
parity	-	-	-	+		
exogenous hormones	+?	+/-	+/-	+	+	
male vasectomy						+?
sexual activity				+		+
hygiene				-		

*for explanation see text;+ positive association; - negative association

The increasing trend in breast cancer incidence is associated with trends in five major lifestyle determinants. Increased caloric intake and alcohol consumption together with decreased physical activity correlates with increased breast cancer risk. In addition, decreasing parity, decreasing total breast feeding time and increasing age at first birth correlates with increased breast cancer risk. Sex

hormone exposure through pharmaceuticals has also been related to increased breast cancer risk. A specific risk may occur in young women. The trends toward earlier menarche and increased sexual activity has stimulated the use of contraceptives by women in their teens. Several recent studies have found an association between contraceptive use below the age of 25 and breast cancer incidence, as well as concomittant changes in epithelial proliferative status and estrogen receptor concentration. In view of the current lifestyle trends more research into this issue is needed.

Ovarian and endometrial cancer show no current trends. The decreasing trend in parity would increase ovarian cancer risk. The increasing trend in infertility treatment with gonadotropins would also increase ovarian cancer risk, whereas increasing longterm contraceptive use would decrease ovarian cancer risk. Endometrial cancer risk seems to increase with increasing caloric intake, with decreasing parity, and with unopposed estrogen exposure, which was the popular postmenopause therapy in the sixties and seventies. Longterm use of combination contraceptives however appears to be protective against endometrial cancer. Other factors will however also play a role, as discussed above.

Although decreasing parity would appear to decrease cervical cancer risk, the decreasing trend in cervical cancer is probably largely attributable to improved hygiene. This effect outweighs other determinants of cervical cancer such as historic DES exposure and increasing sexual activity.

The increase in testicular cancer is associated with decreased physical activity, probably through increased testicular temperature. In addition, maternal lifestyle during pregnancy appears particularly important. DES exposure during pregnancy may have caused congenital malformations which increase testicular cancer risk. Moreover, recent Danish studies have suggested that maternal smoking during pregnancy may be related to testicular cancer. Both maternal smoking and testicular cancer are relatively frequent and increasing in Denmark. In addition, a parallelism was noted between incidences of smoking-related maternal bladder cancer and testis cancer in sons. More research on this association is warranted. Thus, the worldwide increase in testicular cancer is in agreement with changes in three major lifestyle determinants.

Prostate cancer increase is associated with increasing trends in caloric intake, sexual activity and vasectomy. Recent studies have described an association between vasectomy and prostate cancer, which may be mediated by observed effects on sex hormone homeostasis and histopathologic effects. As vasectomy is still gaining popularity as a contraceptive method, more research into this area is needed.

In summary, it is noteworthy that the major lifestyle determinants of reproductive organ cancers are found in two main areas, namely consumptive and reproductive behaviour. Dramatic consumptive changes in the twentieth century with increased caloric intake in the presence of decreased physical activity, and increased alcohol intake and increased female smoking are thought to have promoted reproductive cancers. In addition, profound changes in reproductive behaviour with decreased parity, increased maternal age, increased sexual activity, wide application of various types of sex hormone therapy and contraceptive measures are thought to have contributed to increased reproductive cancer incidences. The current trends in these lifestyle determinants seem to lead away from optimal physiologic conditions for the prevention of human reproductive organ cancer.

The contribution of environmental endocrine disrupters to cancer incidences is difficult to estimate. At present they do not appear as major determinants of reproductive organ cancer. However, the lack of information on actual human exposure to these compounds precludes an assessment of their

current impact on human health. On the other hand, exposure estimates indicate that the endocrine activity of these compounds is generally extremely low as compared to therapeutic and contraceptive preparations (Safe 1995, Golden et al., 1998). In addition, environmental exposure to antiestrogenic compounds may counteract estrogenic compounds. The likelihood of the involvement of endocrine disrupters in reproductive organ cancers can be inferred by relating cancer incidence trends with exposure trends. Waddell (1998) mentions several findings that would render endocrine disrupters unlikely as causes for reproductive cancer. The inverse relationship observed between fruit and vegetable intake and breast cancer has been hypothesized to be related to isoflavonoid intake. These estrogenic compounds would therefore seem to protect against breast cancer, but further research is needed. In addition, the massive intake of the very potent synthetic estrogen DES in the 1940s and 1950s at a time when breast tissue was sensitive to estrogens have not lead to a large and transient increase in the incidence of breast cancer. Furthermore, the application and environmental spreading of PCB's and DDT occurred when reproductive cancer incidences were already increasing, and incidences have not stabilized or decreased upon discontinuation of use and exposure reduction. Taken together, the information currently available does not indicate that endocrine disrupters present an important hazard with respect to reproductive organ cancer. However, human exposure data and mechanistic effect studies on endocrine disrupters are needed before definitive statements can be made. The present literature on determinants of reproductive cancers suggests that lifestyle determinants may play a more prominent role than endocrine disrupter exposure in the determination of trends in reproductive cancer incidences.

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References

Chapter 1: Introduction

- Ashby J, Houthoff E, Kennedy SJ, Stevens J, Bars R, Jekat FW, Campbell P, Van Miller J, Carpanini FM, Randall GL. The challenge posed by endocrine-disrupting chemicals. *Environ Health Perspect* 105(2): 164-169 1997

Chapter 3.1: Breast cancer

CEP: Schottenfeld D, Fraumeni JF Jr. Cancer Epidemiology and Prevention. Oxford University Press 1996

COMA: Nutritional Aspects of the Development of Cancer. Committee on Medical Aspects of Food and Nutrition Policy, Department of Health, UK, 1998.

FNPC: World Cancer Research Fund in association with American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer. American Institute for Cancer Research 1997

NCR: Visser O, Coebergh JWW, Schouten LJ, Van Dijck JAAM. Incidence of cancer in the Netherlands. Sixth report of the Netherlands Cancer Registration 1994

SRK: Signaleringsrapport Kanker, Koningin Wilhelmina Fonds, 1999.

VTV: Ruwaard D, Kramers PGN. Volksgezondheid Toekomst Verkenning. RIVM 1993

Adlercreutz H. Phytoestrogens: epidemiology and a possible role in cancer protection. *Environ Health Perspect* 103(suppl 7): 103-112 1995

Anderson TJ, Battersby S, King RJ, McPherson K, Going JJ. Oral contraceptive use influences resting breast proliferation. *Hum Pathol* 20(12): 1139-1144 1989

Ashby J, Houthoff E, Kennedy SJ, Stevens J, Bars R, Jekat FW, Campbell P, Van Miller J, Carpanini FM, Randall GL. The challenge posed by endocrine-disrupting chemicals. *Environ Health Perspect* 105(2): 164-169 1997

Bernstein L, Ross RK, Lobo RA, Hanisch R, Krailo MD, Henderson BE. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. *Br J Cancer* 55(6): 681-685 1987

Brenner H, Wiebelt H, Ziegler H. [Incidence and prognosis of breast cancer in young women in relation to changes in the risk factor profile]. *Geburtshilfe Frauenheilkd* 50(9): 683-688 1990

Calle EE, Mervis CA, Thun MJ, Rodriguez C, Wingo PA, Heath CW Jr. Diethylstilbestrol and risk of fatal breast cancer in a prospective cohort of US women. *Am J Epidemiol* 144: 645-652 1996

Chie WC, Li CY, Huang CS, Chang KJ, Yen ML, Lin RS. Oral contraceptives and breast cancer risk in Taiwan, a country of low incidence of breast cancer and low use of oral contraceptives. *Int J Cancer* 77(2): 219-223 1998

Colton T, Greenberg ER, Noller K, Resseguie L, Van Bennekom C, Hereen T, Zhang Y. Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. *J Am Med Assoc* 269: 2096-2100 1993

Den Tonkelaar I, De Waard F. Regularity and length of menstrual cycles in women aged 41-46 in relation to breast cancer risk: results from the DOM-project. *Breast Cancer Res Treat* 38(3): 253-258 1996

Djuric Z, Kritschevsky D. Modulation of oxidative DNA damage levels by dietary fat and calories. *Mutation Research* 295: 181-190 1993

Dunn SE, Kari FW, French J, Leininger JR; Travlos G, Wilson R; Barrett JC. Dietary restriction reduces Insulin-like Growth Factor I levels, which modulates apoptosis, cell proliferation and tumor progression in p53-deficient mice. *Cancer Research* 57: 4667-4672 1997

Ebeling K. [Epidemiology of breast cancer]. *Zentralbl Gynakol* 112(5): 253-262 1990

Ferraroni M, Decarli A, Willett WC, Marubini E. Alcohol and breast cancer risk: a case-control study from northern Italy. *Int J Epidemiol* 20(4): 859-864 1991

Frankel S, Gunnell DJ, Peters TJ, Maynard M, Davey-Smith G. Childhood energy intake and adult mortality from cancer: the Boyd Orr Cohort Study. *BMJ* 316(7130): 499-504 1998

Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, Swanson MK, Nemoto T, Graham S. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst* 88(6): 340-348 1996

Golden RJ, Noller KL, Titus-Ernstoff L, Kaufman RH, Mittendorf R, Stillman R, Reese EA. Environmental endocrine modulators and human health: an assessment of the biological evidence. *Critical Reviews in Toxicology* 28(2): 109-227 1998

Graham S, Hellmann R, Marshall J, Freudenheim J, Vena J, Swanson M, Zielezny M, Nemoto T, Stubbe N, Raimondo T. Nutritional epidemiology of postmenopausal breast cancer in western New York. *Am J Epidemiol* 134(6): 552-566 1991

Hatch EE, Palmer JR, Titus-Ernstoff L, Noller KL, Kaufman RH, Mittendorf R, Robboy SJ, Hyer M, Cowan CM, Adam E, Colton T, Hartge P, Hoover RN. Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 280(7): 630-634 1998

Hirohata T, Nomura AM, Hankin JH, Kolonel LN, Lee J. An epidemiologic study on the association between diet and breast cancer. *J Natl Cancer Inst* 78(4): 595-600 1987

Hoffman-Goetz L, Husted J. Exercise and breast cancer: review and critical analysis of the literature. *Can J Appl Physiol* 19(3): 237-252 1994

Horn-Ross PL. Phytoestrogens, body composition and breast cancer. *Cancer Causes and Control* 6: 567-573 1995

Hunter DJ,Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, Fraser GE, Goldbohm RA, Graham S, Howe GR, et al. Cohort studies of fat intake and the risk of breast cancer- a pooled analysis. N Engl. J. Med. 344: 1606, 1996.

Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. *Lancet* 350(9083): 990-994 1997

Johnson JH. Weighing the evidence on the pill and breast cancer. *Fam Plann Perspect* 21(2): 89-92 1989

Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, Hoover R, Taylor PR. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *J Natl Cancer Inst* 79(3): 465-471 1987

Kavlock RJ, Daston GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, Lucier G, Luster M, Mac MJ, Maczka C, Miller R, Moore J, Rolland R, Scott G, Sheehan DM, Sinks T, Tilson HA. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. *Environ Health Perspect* 104 Suppl 4: 715-740 1996

Kritchevsky D. The effect of over- and undernutrition on cancer. *European Journal of Cancer Prevention* 4: 445-451 1995

Kurzer MS, Xu X. Dietary phytoestrogens. *Annu Rev Nutr* 17: 353-381 1997

Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, Folsom AR. Dietary fat and postmenopausal breast cancer. *J Natl Cancer Inst* 84(14): 1092-1099 1992

La Vecchia C, Decarli A, Parazzini F, Gentile A, Negri E, Cecchetti G, Franceschi S. General epidemiology of breast cancer in northern Italy. *Int J Epidemiol* 16(3): 347-355 1987

Li CI, Malone KE, White E, Daling JR. Age when maximum height is reached as a risk factor for breast cancer among young U.S. women. *Epidemiology* 8(5): 559-565 1997

MacMahon B, Trichopoulos D, Brown J, Andersen AP, Aoki K, Cole P, De Waard F, Kauraniemi T, Morgan RW, Purde M, Ravnihar B, Stromby N, Westlund K, Woo NC. Age at menarche, probability of ovulation and breast cancer risk. *Int J Cancer* 29(1): 13-16 1982

Masoro EJ. Dietary restriction and aging. *JAGS* 41: 994-999 1993

Matkovic V, Ilich JZ, Skugor M, Badenhop NE, Goel P, Clairmont A, Klisovic D, Nahhas RW, Landoll JD. Leptin is inversely related to age at menarche in human females. *J Clin Endocrinol Metab* 82(10): 3239-3245 1997

Meirik O, Lund E, Adami HO, Bergstrom R, Christoffersen T, Bergsjo P. Oral contraceptive use and breast cancer in young women. A joint national case-control study in Sweden and Norway. *Lancet* 2(8508): 650-654 1986

Mennes W, Piersma AH. Volksgezondheidsaspecten van 'oestrogene stoffen' in het milieu. RIVM rapport 613320 001 1996

Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. *Am J Epidemiol* 138(4): 217-224 1993

Mills PK, Beeson WL, Phillips RL, Fraser GE. Prospective study of exogenous hormone use and breast cancer in Seventh-day Adventists. *Cancer* 64(3): 591-597 1989

Olsson H, Lindahl B, Ranstam J, Borg A, Ferno M, Norgren A. Permanent alterations induced in plasma prolactin and estrogen receptor concentration in benign and malignant tissue of women who started oral contraceptive use at an early age. *Anticancer Res* 7(4B): 853-856 1987

Olsson H, Moller TR, Ranstam J. Early oral contraceptive use and breast cancer among premenopausal women: final report from a study in southern Sweden. *J Natl Cancer Inst* 81(13): 1000-1004 1989

Paul C, Skegg DC, Spears GF. Oral contraceptives and risk of breast cancer. *Int J Cancer* 46(3): 366-373 1990

McPherson K. Combined progestin and estrogen (oral) and other forms of hormonal contraception. *Current Opinion in Obstetrics and Gynecology* 3: 486-490 1991

Pike MC, Henderson BE, Casagrande JT, Rosario I, Gray GE. Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *Br J Cancer* 43(1): 72-76 1981

Rao GN. Influence of diet on tumors of hormonal tissues. In: Cellular and molecular mechanisms of hormonal carcinogenesis: environmental influences; Chapter 3. Edited by Huff J, Boyd J and Barrett JC; Wiley-Liss, Inc. 1996

Richardson S, Gerber M, Cenee S. The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in southern France. *Int J Cancer* 48(1): 1-9 1991

Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. *Cancer Causes Control* 4(1): 29-37 1993

Safe SH. Environmental and dietary estrogens and human health - Is there a problem?. *Environ Health Perspect* 103: 346-351 1995

Tannenbaum A. The genesis and growth of tumors. II. Effects of caloric restriction per se. *Cancer Res* 2: 460-467 1942

Thorling EB. Obesity, fat intake, energy balance, exercise and cancer risk. A review. *Nutrition Research* 16(2): 315-368 1996

UK Natl Case-Control Study Group. Oral contraceptive use and breast cancer risk in young women. *Lancet* 1(8645): 973-982 1989

Van den Brandt PA, Dirx MJ, Ronckers CM, Van den Hoogen P, Goldbohm RA. Height, weight, weight change and postmenopausal breast cancer risk: The Netherlands Cohort Study. *Cancer Causes Control* 8(1): 39-47 1997

Van den Brandt PA, Van 't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJ, Sturmans F. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Res* 53(1): 75-82 1993

Van 't Veer P, Kolb CM, Verhoef P, Kok FJ, Schouten EG, Hermus RJ, Sturmans F. Dietary fiber, beta-carotene and breast cancer: results from a case-control study. *Int J Cancer* 45(5): 825-828 1990

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17: 173-191 1998

Weindruch R. Effect of caloric restriction on age-associated cancers. *Experimental Gerantology* 27: 575-581 1992

Weiss HA, Potischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB. Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology* 8(2): 181-187 1997

Welsch CW. Relationship between dietary fat and experimental mammary tumorigenesis: a review and critique. *Cancer Res* 52(7 Suppl): 2040s-2048s 1992

White E, Malone KE, Weiss NS, Daling JR. Breast cancer among young U.S. women in relation to oral contraceptive use. *J Natl Cancer Inst* 86(7): 505-514 1994

Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, Rosner B, Hennekens CH, Speizer FE. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *JAMA* 268(15): 2037-2044 1992

Ziegler RG, Hoover RN, Nomura AM, West DW, Wu AH, Pike MC, Lake AJ, Horn-Ross PL, Kolonel LN, Siiteri PK, Fraumeni JF Jr. Relative weight, weight change, height, and breast cancer risk in Asian-American women. *J Natl Cancer Inst* 88(10): 650-660 1996

Chapter 3.2: Ovarian cancer

CEP: Schottenfeld D, Fraumeni JF Jr. Cancer Epidemiology and Prevention. Oxford University Press 1996

COMA: Nutritional Aspects of the Development of Cancer. Committee on Medical Aspects of Food and Nutrition Policy, Department of Health, UK, 1998.

FNPC:. World Cancer Research Fund in association with American Institute for Cancer Research Food, Nutrition and the Prevention of Cancer. American Institute for Cancer Research 1997

NCR: Visser O, Coebergh JWW, Schouten LJ, Van Dijck JAAM. Incidence of cancer in the Netherlands. Sixth report of the Netherlands Cancer Registration 1994

Cuzick J. Medicinal drugs with hormonal activity as chemopreventive agents. *IARC Sci Publ* 139: 99-116 1996

Hulka BS. Epidemiologic analysis of breast and gynecologic cancers. *Prog Clin Biol Res* 396: 17-29 1997

Schiffenbauer YS, Abramovitch R, Meir G, Nevo N, Holzinger M, Itin A, Keshet E, Neeman M. Loss of ovarian function promotes angiogenesis in human ovarian carcinoma. *Proc Natl Acad Sci USA* 94(24): 13203-13208 1997

Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker JG. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil Steril* 65(1): 13-18 1996

Tokuoka S, Kawai K, Shimizu Y, Inai K, Ohe K, Fujikura T, Kato H. Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950-80. *J Natl Cancer Inst* 79(1): 47-57 1987

La Vecchia C, Tavani A, Franceschi S, Parazzini F. Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 14(4): 260-272 1996

Venn A, Watson L, Lumley J, Giles G, King C, Healy D. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet* 346(8981): 995-1000 1995

Verhoeven DT, Goldbohm RA, Van Poppel G, Verhagen H, Van den Brandt PA. Epidemiological studies on brassica vegetables and cancer risk. *Cancer Epidemiol Biomarkers Prev* 5(9): 733-748 1996

Westhoff C. Ovarian cancer. *Annu Rev Public Health* 17: 85-96 1996

Chapter 3.3: Endometrial cancer

CEP: Schottenfeld D, Fraumeni JF Jr. Cancer Epidemiology and Prevention. Oxford University Press 1996

COMA: Nutritional Aspects of the Development of Cancer. Committee on Medical Aspects of Food and Nutrition Policy, Department of Health, UK, 1998.

FNPC: World Cancer Research Fund in association with American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer. American Institute for Cancer Research 1997

NCR: Visser O, Coebergh JWW, Schouten LJ, Van Dijck JAAM. Incidence of cancer in the Netherlands. Sixth report of the Netherlands Cancer Registration 1994

Cuzick J. Medicinal drugs with hormonal activity as chemopreventive agents. *IARC Sci Publ* (139): 99-114 1996

Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, Kolonel LN. Diet, body size, physical activity and the risk of endometrial cancer. *Cancer Res* 57(22): 5077-5085 1997

Green PK, Weiss NS, McKnight B, Voigt LF, Beresford SA. Risk of endometrial cancer following cessation of menopausal hormone use (Washington, United States). *Cancer Causes Control* 7(6): 575-580 1996

McPherson CP, Sellers TA, Potter JD, Bostick RM, Folsom AR. Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. *Am J Epidemiol* 143(12): 1195-1202 1996

Rao GN. Influence of diet on tumors of hormonal tissues. In: Cellular and molecular mechanisms of hormonal carcinogenesis: environmental influences; Chapter 3. Edited by Huff J, Boyd J and Barrett JC; Wiley-Liss, Inc. 1996

Stanford JL, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Hoover RN. Oral contraceptives and endometrial cancer: do other risk factors modify the association?. *Int J Cancer* 54(2): 243-248 1993

Sulak-PJ. Endometrial cancer and hormone replacement therapy. Appropriate use of progestins to oppose endogenous and exogenous estrogen. *Endocrinol Metab Clin North Am* 26(2): 399-412 1997

Thorling EB. Obesity, fat intake, energy balance, exercise and cancer risk. A review. *Nutrition Research* 16(2): 315-368 1996

La Vecchia C, Tavani A, Franceschi S, Parazzini F. Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 14(4): 260-272 1996

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17: 173-191 1998

Chapter 3.4: Cervical cancer

CEP: Schottenfeld D, Fraumeni JF Jr. Cancer Epidemiology and Prevention. Oxford University Press 1996

COMA: Nutritional Aspects of the Development of Cancer. Committee on Medical Aspects of Food and Nutrition Policy, Department of Health, UK, 1998.

FNPC: World Cancer Research Fund in association with American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer. American Institute for Cancer Research 1997

NCR: Visser O, Coebergh JWW, Schouten LJ, Van Dijck JAAM. Incidence of cancer in the Netherlands. Sixth report of the Netherlands Cancer Registration 1994

Biswas LN, Manna B, Maiti PK, Sengupta S. Sexual risk factors for cervical cancer among rural Indian women: a case-control study. *Int J Epidemiol* 26(3): 491-495 1997

Bjorge T, Kravdal O. Reproductive variables and risk of uterine cervical cancer in Norwegian registry data. *Cancer Causes Control* 7(3): 351-357 1996

Bosch FX, Munoz N, de Sanjose S. Human papillomavirus and other risk factors for cervical cancer. *Biomed Pharmacother* 51(6-7): 268-275 1997

Boyd J, Takahashi H, Waggoner SE, Jones LA, Hajek RA, Wharton JT, Liu FS, Fujino T, Barrett JC, McLachlan JA. Molecular genetic analysis of clear cell adenocarcinomas of the vagina and cervix associated and unassociated with diethylstilbestrol exposure in utero. *Cancer* 77(3): 507-513 1996

Hatch EE, Palmer JR, Titus-Ernstoff L, Noller KL, Kaufman RH, Mittendorf R, Robboy SJ, Hyer M, Cowan CM, Adam E, Colton T, Hartge P, Hoover RN. Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 280(7): 630-634 1998

Hernandez-Avila M, Lazcano-Ponce EC, Berumen-Campos J, Cruz-Valdez A, Alonso-de Ruiz PP, Gonzalez-Lira G. Human papilloma virus 16-18 infection and cervical cancer in Mexico: a case-control study. *Arch Med Res* 28(2): 265-271 1997

Herrero R. Epidemiology of cervical cancer. *J Natl Cancer Inst Monogr* (21): 1-6 1996

Morris M, Tortolero-Luna G, Malpica A, Baker VV, Cook E, Johnson E, Follen-Mitchell M. Cervical intraepithelial neoplasia and cervical cancer. *Obstet Gynecol Clin North Am* 23(2): 347-410 1996

Nonnenmacher B, Hubbert NL, Kirnbauer R, Shah KV, Munoz N, Bosch FX, de Sanjose S, Viscidi R, Lowy DR, Schiller JT. Serologic response to human papillomavirus type 16 (HPV-16) virus-like particles in HPV-16 DNA-positive invasive cervical cancer and cervical intraepithelial neoplasia grade III patients and controls from Colombia and Spain. *J Infect Dis* 172(1): 19-24 1995

Phillips AN, Smith GD. Cigarette smoking as a potential cause of cervical cancer: has confounding been controlled? *Int J Epidemiol* 23(1): 42-49 1994

Robboy SJ, Young RH, Welch WR, Truslow GY, Prat J, Herbst AL, Scully RE. Atypical vaginal adenosis and cervical ectropion. Association with clear cell adenocarcinoma in diethylstilbestrol-exposed offspring. *Cancer* 54(5): 869-875 1984
of:
Robboy SJ, Noller KL, O'Brien P, Kaufman RH, Townsend D, Barnes AB, Gundersen J, Lawrence WD, Bergstrahl E, McGorray S. Increased incidence of cervical and vaginal dysplasia in 3,980 diethylstilbestrol-exposed young women. Experience of the National Collaborative Diethylstilbestrol Adenosis Project. *JAMA* 252(21): 2979-2983 1984

Storey A, Thomas M, Kalita A, Harwood C, Gardiol D, Mantovani F, Breuer J, Leigh IM, Matlashewski G, Banks L. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. *Nature* 393(6682): 229-234 1998

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17: 173-191 1998

Chapter 3.5: Testis cancer

CEP: Schottenfeld D, Fraumeni JF Jr. Cancer Epidemiology and Prevention. Oxford University Press 1996

NCR: Visser O, Coebergh JWW, Schouten LJ, Van Dijck JAAM. Incidence of cancer in the Netherlands. Sixth report of the Netherlands Cancer Registration 1994

Anthony MS, Clarkson TB, Hughes CL Jr, Morgan TM, Burke GL. Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys. *J Nutr* 126(1): 43-50 1996

Bosland MC. Hormonal factors in carcinogenesis of the prostate and testis in humans and in animal models. *Prog Clin Biol Res* 394: 309-352 1996

Braun MM, Ahlbom A, Floderus B, Brinton LA, Hoover RN. Effect of twinship on incidence of cancer of the testis, breast and other sites (Sweden). *Cancer Causes Control* 6(6): 519-524 1995

Clemmesen J. [Is smoking during pregnancy a cause of testicular cancer?] *Ugeskr Laeger* 159(46): 6815-6819 1997

Davies TW, Palmer CR, Ruja E, Lipscombe JM. Adolescent milk, dairy product and fruit consumption and testicular cancer. *Br J Cancer* 74(4): 657-660 1996

De Waal WJ, Vreeburg JT, Bekkering F, De Jong FH, De Muinck Keizer Schrama SM, Drop SL, Weber RF. High dose testosterone therapy for reduction of final height in constitutionally tall boys: does it influence testicular function in adulthood? *Clin Endocrinol Oxf* 43(1): 87-95 1995

Gallagher RP, Huchcroft S, Phillips N, Hill GB, Coldman AJ, Coppin C, Lee T. Physical activity, medical history and risk of testicular cancer (Alberta and British Columbia, Canada). *Cancer Causes Control* 6(5): 398-406 1995

Giwercman A, Thomsen JK, Hertz J, Berthelsen JG, Jensen V, Meinecke B, Thormann L, Storm HH, Skakkebaek NE. Prevalence of carcinoma in situ of the testis in 207 oligozoospermic men from infertile couples: prospective study of testicular biopsies. *BMJ* 315: 989-991 1997

Heimdal K, Andersen TI, Skrede M, Fossa SD, Berg K, Borresen AL. Association studies of estrogen receptor polymorphisms in a Norwegian testicular cancer population. *Cancer Epidemiol Biomarkers Prev* 4(2): 123-126 1995

Jensen TK, Toppari J, Keiding N, Skakkebaek NE. Do environmental estrogens contribute to the decline in male reproductive health? *Clin Chem* 41(12 Pt 2): 1896-1901 1995

Kelty P, Frazier H, O'Connell K, Ghosh BC. Germ cell testis cancer: 15-year review. *J Surg Oncol* 62(1): 30-33 1996

McBride ML, Van den Steen N, Lamb CW, Gallagher RP. Maternal and gestational factors in cryptorchidism. *Int J Epidemiol* 20(4): 964-970 1991

Moller H, Knudsen LB, Lynge E. Risk of testicular cancer after vasectomy: cohort study of over 73,000 men. *BMJ* 309(6950): 295-299 1994

Oliver RT. Testis cancer. *Curr Opin Oncol* 9(3): 287-294 1997

Petersen PM, Giwercman A, Skakkebaek NE, Rorth M. Gonadal function in men with testicular cancer. *Semin Oncol* 25(2): 224-233 1998

Prener A, Engholm G, Jensen OM. Genital anomalies and risk for testicular cancer in Danish men. *Epidemiology* 7(1): 14-19 1996

Rajpert De Meyts E, Skakkebaek NE. Immunohistochemical identification of androgen receptors in germ cell neoplasia. *J Endocrinol* 135(2): R1-4 1992

Sonnenschein C, Soto AM, Fernandez MF, Olea N, Olea Serrano MF, Ruiz Lopez MD. Development of a marker of estrogenic exposure in human serum. *Clin Chem* 41(12 Pt 2): 1888-1895 1995

Swerdlow AJ, Higgins CD, Pike MC. Risk of testicular cancer in cohort of boys with cryptorchidism. *BMJ* 314(7093): 1507-1511 1997

United Kingdom Testicular Cancer Study Group. Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility and exercise. *BMJ* 308(6941): 1393-1399 1994

Valencia Sanchez A, Ortega Corona BG, Campos Lara G, Ponce Monter H. Environmental temperature and cryptorchidism: effects on pregnenolone-sulfatase of mice testicular tissue. *Arch Androl* 36(3): 233-238 1996

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17(2): 173-191 1998

Walker AH, Bernstein L, Warren DW, Warner NE, Zheng X, Henderson BE. The effect of in utero ethinyl oestradiol exposure on the risk of cryptorchid testis and testicular teratoma in mice. *Br J Cancer* 62(4): 599-602 1990

Zhang ZF, Vena JE, Zielezny M, Graham S, Haughey BP, Brasure J, Marshall JR. Occupational exposure to extreme temperature and risk of testicular cancer. *Arch Environ Health* 50(1): 13-18 1995

Zheng T, Holford TR, Ma Z, Ward BA, Flannery J, Boyle P. Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935-1992. *Int J Cancer* 65(6): 723-729 1996

Chapter 3.6: Prostate cancer

CEP: Schottenfeld D, Fraumeni JF Jr. Cancer Epidemiology and Prevention. Oxford University Press 1996

COMA: Nutritional Aspects of the Development of Cancer. Committee on Medical Aspects of Food and Nutrition Policy, Department of Health, UK, 1998.

FNPC: World Cancer Research Fund in association with American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer. American Institute for Cancer Research 1997

NCR: Visser O, Coebergh JWW, Schouten LJ, Van Dijck JAAM. Incidence of cancer in the Netherlands. Sixth report of the Netherlands Cancer Registration 1994

VTV: Ruwaard D, Kramers PGN. Volksgezondheid Toekomst Verkenning. RIVM 1993

Adlercreutz H, Markkanen H, Watanabe S. Plasma concentrations of phyto-oestrogens in Japanese men. *Lancet* 342(8881): 1209-1210 1993

Ahluwalia B, Jackson MA, Jones GW, Williams AO, Rao MS, Rajguru S. Blood hormone profiles in prostate cancer patients in high-risk and low-risk populations. *Cancer* 48(10): 2267-2273 1981

Andersson SO, Wolk A, Bergstrom R, Giovannucci E, Lindgren C, Baron J, Adami HO. Energy, nutrient intake and prostate cancer risk: a population-based case-control study in Sweden. *Int J Cancer* 68(6): 716-722 1996a

Andersson SO, Baron J, Bergstrom R, Lindgren C, Wolk A, Adami HO. Lifestyle factors and prostate cancer risk: a case-control study in Sweden. *Cancer Epidemiol Biomarkers Prev* 5(7): 509-513 1996b

Andersson SO, Wolk A, Bergstrom R, Adami HO, Engholm G, Englund A, Nyren O. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers. *J Natl Cancer Inst* 89(5): 385-389 1997

Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). *Cancer Causes Control* 6(3): 235-239 1995

Catalona WJ. Management of cancer of the prostate. *N Engl J Med* 331(15): 996-1004 1994

Cerhan JR, Torner JC, Lynch CF, Rubenstein LM, Lemke JH, Cohen MB, Lubaroff DM, Wallace RB. Association of smoking, body mass and physical activity with risk of prostate cancer in the Iowa 65+ Rural Health Study (United States). *Cancer Causes Control* 8(2): 229-238 1997

Coughlin SS, Neaton JD, Sengupta A. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 143(10): 1002-1006 1996

Dong JT, Lamb PW, Rinker Schaeffer CW, Vukanovic J, Ichikawa T, Isaacs JT, Barrett JC. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. *Science* 268(5212): 884-886 1995

Ellis L, Nyborg H. Racial/ethnic variations in male testosterone levels: a probable contributor to group differences in health. *Steroids* 57(2): 72-75 1992

Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ. Prospective study of plasma fatty acids and risk of prostate cancer [published erratum appears in J Natl Cancer Inst 1994 86(9): 728]. *J Natl Cancer Inst* 86(4): 281-286 1994

Ghadirian P, Lacroix A, Maisonneuve P, Perret C, Drouin G, Perrault JP, Beland G, Rohan TE, Howe GR. Nutritional factors and prostate cancer: a case-control study of French Canadians in Montreal, Canada. *Cancer Causes Control* 7(4): 428-436 1996

Giles G, Ireland P. Diet, nutrition and prostate cancer. *Int J Cancer* Suppl 10: 13-17 1997

Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 85(19): 1571-1579 1993

Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst* 87(23): 1767-1776 1995

Giovannucci E. How is individual risk for prostate cancer assessed? *Hematol Oncol Clin North Am* 10(3): 537-548 1996

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Height, body weight and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 6(8): 557-563 1997a

Giovannucci E, Stampfer MJ, Krithivas K, Brown M, Dahl D, Brufsky A, Talcott J, Hennekens CH, Kantoff PW. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer [published erratum appears in Proc Natl Acad Sci USA 1997 94(15): 8272]. *Proc Natl Acad Sci USA* 94(7): 3320-3323 1997b

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Diabetes mellitus and risk of prostate cancer (United States). *Cancer Causes Control* 9(1): 3-9 1998

Gronberg H, Damber L, Damber JE. Total food consumption and body mass index in relation to prostate cancer risk: a case-control study in Sweden with prospectively collected exposure data. *J Urol* 155(3): 969-974 1996

Hayes RB, Brown LM, Schoenberg JB, Greenberg RS, Silverman DT, Schwartz AG, Swanson GM, Benichou J, Liff JM, Hoover RN, Pottern LM. Alcohol use and prostate cancer risk in US blacks and whites. *Am J Epidemiol* 143(7): 692-697 1996

Henderson BE, Bernstein L, Ross RK, Depue RH, Judd HL. The early in utero oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer* 57(2): 216-218 1988

Hiatt RA, Armstrong MA, Klatsky AL, Sidney S. Alcohol consumption, smoking and other risk factors and prostate cancer in a large health plan cohort in California (United States). *Cancer Causes Control* 5(1): 66-72 1994

Hirayama T. Life-style and cancer: from epidemiological evidence to public behavior change to mortality reduction of target cancers. *J Natl Cancer Inst Monogr* (12): 65-74 1992

Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 57(3): 326-331 1988

Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HT, Blot WJ. Diet, tobacco use and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. *Cancer Res* 50(21): 6836-6840 1990a

Hsing AW, Comstock GW, Abbey H, Polk BF. Serologic precursors of cancer. Retinol, carotenoids and tocopherol and risk of prostate cancer. *J Natl Cancer Inst* 82(11): 941-946 1990b

Imai K, Fukabori Y, Yamanaka H. [Etiology of prostate cancer and significance of screening for early prostate cancer]. *Gan To Kagaku Ryoho* 23(4): 403-406 1996

Kao PC, P'eng FK. How to reduce the risk factors of osteoporosis in Asia. *Chung Hua I Hsueh Tsa Chih Taipei* 55(3): 209-213 1995

Kaul L, Heshmat MY, Kovi J, Jackson MA, Jackson AG, Jones GW, Edson M, Enterline JP, Worrell RG, Perry SL. The role of diet in prostate cancer. *Nutr Cancer* 9(2-3): 123-128 1987

Key T. Risk factors for prostate cancer. *Cancer Surv* 23: 63-77 1995

Knekt P, Aromaa A, Maatela J, Aaran RK, Nikkari T, Hakama M, Hakulinen T, Peto R, Teppo L. Serum vitamin A and subsequent risk of cancer: cancer incidence follow-up of the Finnish Mobile Clinic Health Examination Survey. *Am J Epidemiol* 132(5): 857-870 1990

Kolonel LN. Nutrition and prostate cancer. *Cancer Causes Control* 7(1): 83-44 1996

Lee IM, Paffenbarger RS Jr, Hsieh CC. Physical activity and risk of prostatic cancer among college alumni. *Am J Epidemiol* 135(2): 169-179 1992

Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T. Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology* 5(3): 276-282 1994

Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle and prostate cancer in Adventist men. *Cancer* 64(3): 598-604 1989

Murphy GP, Natarajan N, Pontes JE, Schmitz RL, Smart CR, Schmidt JD, Mettlin C. The national survey of prostate cancer in the United States by the American College of Surgeons. *J Urol* 127(5): 928-934 1982

Polednak AP. College athletics, body size and cancer mortality. *Cancer* 38(1): 382-387 1976

Ripple MO, Henry WF, Rago RP, Wilding G. Prooxidant-antioxidant shift induced by androgen treatment of human prostate carcinoma cells. *J Natl Cancer Inst* 89(1): 40-48 1997

Rose DP, Boyar AP, Wynder EL. International comparisons of mortality rates for cancer of the breast, ovary, prostate and colon, and per capita food consumption. *Cancer* 58(11): 2363-2371 1986

Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC, Henderson BE. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. *Lancet* 339(8798): 887-889 1992

Schwartz GG, Hill CC, Oeler TA, Becich MJ, Bahnson RR. 1,25-Dihydroxy-16-ene-23-yne-vitamin D3 and prostate cancer cell proliferation in vivo. *Urology* 46(3): 365-369 1995

Severson RK, Grove JS, Nomura AM, Stemmermann GN. Body mass and prostatic cancer: a prospective study. *BMJ* 297(6650): 713-715 1988

Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective analysis of physical activity and cancer. *Am J Epidemiol* 130(3): 522-529 1989a

Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* 49(7): 1857-1860 1989b

Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* 66(4): 673-679 1992

Shibata A, Whittemore AS. Genetic predisposition to prostate cancer: possible explanations for ethnic differences in risk. *Prostate* 32(1): 65-72 1997

Slawin K, Kadmon D, Park SH, Scardino PT, Anzano M, Sporn, MB, Thompson TC. Dietary fenretinide, a synthetic retinoid, decreases the tumor incidence and the tumor mass of ras+myc-induced carcinomas in the mouse prostate reconstitution model system. *Cancer Res* 53(19): 4461-4465 1993

Snowdon DA, Phillips RL, Choi W. Diet, obesity and risk of fatal prostate cancer. *Am J Epidemiol* 120(2): 244-250 1984

Thompson MM, Garland C, Barrett Connor E, Khaw KT, Friedlander NJ, Wingard DL. Heart disease risk factors, diabetes and prostatic cancer in an adult community. *Am J Epidemiol* 129(3): 511-517 1989

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17(2): 173-191 1998

Whittemore AS, Wu AH, Kolonel LN, John EM, Gallagher RP, Howe GR, West DW, Teh CZ, Stamey T. Family history and prostate cancer risk in black, white and Asian men in the United States and Canada. *Am J Epidemiol* 141(8): 732-740 1995a

Whittemore AS, Kolonel LN, Wu AH, John EM, Gallagher RP, Howe GR, Burch JD, Hankin J, Dreon DM, West DW et al. Prostate cancer in relation to diet, physical activity and body size in blacks, whites and Asians in the United States and Canada. *J Natl Cancer Inst* 87(9): 652-661 1995b

Chapter 4: Lifestyle determinants

NiDi: Nederlands Interdisciplinair Demografisch Instituut, Bevolkingsvraagstukken in Nederland anno 1997, Van Nimwegen, Beets, 1997

VTV: Ruwaard D, Kramers PGN. Volksgezondheid Toekomst Verkenning. RIVM 1993

Mack and Mohadjer, 1985

Brown WA, Monti PM, Corriveau DP. Serum testosterone and sexual activity and interest in men. *Arch Sex Behav* 7(2): 97-103 1978

Brundtland GH, Liestol K, Walloe L. Height, weight and menarcheal age of Oslo schoolchildren during the last 60 years. *Ann Hum Biol* 7(4): 307-322 1980

Cameron N. The growth of London schoolchildren 1904-1966: an analysis of secular trend and intra-county variation. *Ann Hum Biol* 6(6): 505-525 1979

Carr BR. HRT management: the American experience. *Eur J Obstet Gynecol Reprod Biol* 64 Suppl: S17-20 1996

Colborn T, Vom-Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environ Health Perspect* 101(5): 378-384 1993

Cuijpers CEJ, Zeilmaker MJ, Van der Molen GW, Slob W, Lebret E. Developments in infant exposure to dioxins, furans and PCBs in breast milk and potential health concequences, in the Netherlands. *Report no. 529102007 of National Institute of Public Health and the Environment* 1997

Dacou-Voutetakis C, Klontza D, Lagos P, Tzonou A, Katsarou E, Antoniadis S, Papazisis G, Papadopoulos G, Matsaniotis N. Age of pubertal stages including menarche in Greek girls. *Ann Hum Biol* 10(6): 557-563 1983

Flint M. Is there a secular trend in age of menopause? *Maturitas* 1(2): 133-139 1978

Forste R, Tanfer K, Tedrow L. Sterilization among currently married men in the United States, 1991. *Fam Plann Perspect* 27(3): 100-107, 122 1995

Harrison PTC. IEH assessment on environmental oestrogens; consequences to human health and wildlife. *Medical Research Counsil, Institute for Environmental Health* 1995

Helm P, Grolund L. A halt in the secular trend towards earlier menarche in Denmark. *Acta Obstet Gynecol Scand* 77(2): 198-200 1998

Hemminki E, Topo P. Prescribing of hormone therapy in menopause and postmenopause. *J Psychosom Obstet Gynaecol* 18(2): 145-157 1997

Hoel DG, Wakabayashi T, Pike MC. Secular trends in the distributions of the breast cancer risk factors--menarche, first birth, menopause and weight--in Hiroshima and Nagasaki, Japan. *Am J Epidemiol* 118(1): 78-89 1983

Liestol K. Social conditions and menarcheal age: the importance of early years of life. *Ann Hum Biol* 9(6): 521-537 1982

Loukid M, Baali A, Hilali MK. Secular trend in age at menarche in Marrakesh (Morocco). *Ann Hum Biol* 23(4): 333-335 1996

Mack GA, Mohadjer L. Baseline Estimates and Time Trends for Beta-Benzene Hexachloride, Hexachlorobenzene and Polychlorinated Biphenyls in Human Adipose Tissue 1970-1983. Environmental Protection Agency, Washington, DC. Office of Pesticides and Toxic Substances. Govt Reports Announcements & Index (GRA&I) 10 1985

McKinlay SM, Bifano NL, McKinlay JB. Smoking and age at menopause in women. *Ann Intern Med* 103(3): 350-356 1985

McKinlay SM. The normal menopause transition: an overview. *Maturitas* 23(2): 137-145 1996

Meredith HV. Secular change in sitting height and lower limb height of children, youths and young adults of Afro-black, European and Japanese ancestry. *Growth* 42(1): 37-41 1978

Oduntan SO, Ayeni O, Kale OO. The age of menarche in Nigerian girls. *Ann Hum Biol* 3(3): 269-274 1976

Parazzini F, Negri E, La Vecchia C. Reproductive and general lifestyle determinants of age at menopause. *Maturitas* 15(2): 141-149 1992

Paul C, Skegg DC, Smeijers J, Spears GF. Contraceptive practice in New Zealand. *N Z Med J* 101(859): 809-813 1988

Rappe C. Review of the dioxin problem. *IARC Sci Publ* (108): 1-3 1991

Robinson PE, Mack GA, Remmers J, Levy R, Mohadjer L. Trends of PCB, hexachlorobenzene and beta-benzene hexachloride levels in the adipose tissue of the U.S. population. *Environ Res* 53(2): 175-192 1990

Roche AF. Secular trends in human growth, maturation and development. *Monogr Soc Res Child Dev* 44(3-4): 1-120 1979

Rosenberg M. Menarcheal age for Norwegian women born 1830-1960. *Ann Hum Biol* 18(3): 207-219 1991

Safe SH. Environmental and dietary estrogens and human health: is there a problem? *Environ Health Perspect* 103(4): 346-351 1995

Tryggvadottir L, Tulinius H, Larusdottir M. A decline and a halt in mean age at menarche in Iceland. *Ann Hum Biol* 21(2): 179-186 1994

Tsitouras PD, Martin CE, Harman SM. Relationship of serum testosterone to sexual activity in healthy elderly men. *J Gerontol* 37(3): 288-293 1982

Tsuzaki S, Matsuo N, Ogata T, Osano M. Lack of linkage between height and weight and age at menarche during the secular shift in growth of Japanese children. *Ann Hum Biol* 16(5): 429-436 1989

Van Noord PA, Dubas JS, Dorland M, Boersma H, Te Velde E. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity and lifestyle factors. *Fertil Steril* 68(1): 95-102 1997

Venrooy-Ijsselmuiden ME, Smeets HJ. The secular trend in age at menarche in the Netherlands. *Ann Hum Biol* 3(3): 283-284 1976

Vercauteren M, Susanne C. The secular trend of height and menarche in Belgium: are there any signs of a future stop? *Eur J Pediatr* 144(4): 306-309 1985

Veronesi FM, Gueresi P. Trend in menarcheal age and socioeconomic influence in Bologna (northern Italy). *Ann Hum Biol* 21(2): 187-196 1994

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17(2): 173-191 1998

Chapter 5: General Discussion

VTV: Ruwaard D, Kramers PGN. Volksgezondheid Toekomst Verkenning. RIVM 1993

Golden RJ, Noller KL, Titus-Ernstoff L, Kaufman RH, Mittendorf R, Stillman R, Reese EA. Environmental endocrine modulators and human health: an assessment of the biological evidence. *Critical Reviews in Toxicology* 28(2): 109-227 1998

Safe SH. Environmental and dietary estrogens and human health: is there a problem? *Environ Health Perspect* 103(4): 346-351 1995

Waddell WJ. Epidemiological studies and effects of environmental estrogens. *International Journal of Toxicology* 17(2): 173-191 1998