

# Conditions *in utero* and cancer risk

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## INTRODUCTION

Most cancer cases are diagnosed after the age of 60. Over the past years, however, increasing evidence has supported the notion that conditions *in utero* or early childhood may be of importance for the disease process. Such hypotheses have been examined and discussed for other chronic diseases,<sup>1</sup> and in fact also for specific types of cancer.<sup>2</sup> Already in 1877, the German pathologist Julius Cohnheim hypothesised that events *in utero* could be related to cancer later in life, and he pinpointed the similarity between the cancer cells and embryonic cells.<sup>3</sup>

Based on historical analysis of infant mortality in two municipalities in Norway in 1814-78, Fure<sup>4</sup> suggested that mothers themselves born in socio-economic prosperous times, gave birth to children with a lower rate of neonatal deaths than those of mothers born under less favourable conditions. This study emphasises the possibility that exposures *in utero* in one generation may influence the vitality even in later generations. By the same token, in a Swedish cohort of individuals born in 1928 the relation between parental economic resources and mortality among elderly was studied.<sup>5</sup> The rich information on individual income throughout the entire life cycle allowed the researchers to construct a measure of lifetime earnings. A competing risk analysis showed a strong relation between parental income and death from cancer while own income later in life seemed more important for circulatory diseases as cause of death.

In 2001, the median age for all cancer types in Norway was 70 years for men and 69 years for women. Nine percent of the male and 14% of the female cases were diagnosed before age 50, and only 2% were diagnosed before age 30 for both genders.<sup>6</sup> Although inherited gene alterations are expected to be more prevalent in younger than older cases, it is notable that even the young cases have lived for a long time exposed to a variety of possibly harmful factors before the cancer is diagnosed. Another observation further emphasising the length of the disease process, comes from migration studies, which indicate that adoption of the cancer rates in the first generation depends on the age at migration.<sup>7</sup>

Cancer is generally believed to arise from a single

cell and is initiated when the cell has experienced at least two genetic alterations, although other theories exist.<sup>8</sup> The critical genes are basically oncogenes, tumour suppressor genes and DNA repair genes. In the case of retinoblastoma, Knudson<sup>9</sup> suggested that gene alterations affecting both alleles of the same gene (designated Rb) were necessary to initiate cancer. In colon cancer, a similar initiation seems to be necessary, but seven or eight gene alterations are probably needed.<sup>10</sup> It is not known if these alterations demand a special order of sequence. This indicates that it takes time to accumulate enough genetic damage<sup>11</sup> and to develop a detectable cancer. Even for lung cancer where smoking is an established strong causal factor, the median age at diagnosis is 69 years. Only a minor proportion of the heavy smokers develop lung cancer during their lifetime,<sup>12</sup> indicating an individual susceptibility for cancer. This susceptibility may be inherited<sup>13</sup> or acquired *in utero* or in early life when the organs are still developing. The biological mechanisms behind heterogeneous susceptibility and the relation to environmental and lifestyle factors are not well understood. Hypothetically they have been linked to factors influencing the number of cells at risk, events that may cause genetic instability, increased risk of essential mutations during the development of target organs, or a gene-environment interaction during intrauterine life.<sup>14</sup> These hypotheses are not mutually exclusive.

After the initiation of the first cancer cell, the tumour has to grow to a detectable size before it could be diagnosed. A tumour that has doubled its size 30 times, will be about 1 cm<sup>3</sup>. Depending on the type of cancer, the tumour size will usually double a few more times before giving rise to clinical symptoms. The growth rate depends on the frequencies of mitosis and apoptosis, but also on the rate of angiogenesis. These important events in the disease process can also hypothetically be linked to conditions *in utero*, but to our knowledge, studies have not been undertaken to shed light on these issues.

The *in utero* hypothesis implies that the disease process in a broad sense may last several decades, which makes it difficult to design relevant epidemiological studies. Data on exposures and conditions *in utero* way back in time are obviously limited, and therefore most of the evidence for an association

between *in utero* exposures and cancer risk is based on indirect observations. Below, we summarise the evidence regarding the association between intrauterine exposure and testicular and breast cancer, the two cancer sites most studied so far in this regard. In addition, epidemiological findings for other types of cancer are addressed in a more general manner.

## TESTICULAR CANCER (TC)

The incidence rate of TC in Caucasian men in at least Europe and North America, has increased several fold over the past 50 years.<sup>15,16</sup> Few other cancer forms have shown a similar rise in incidence rate during this period, and this rapid change within a couple of generations suggests that exogenous rather than genetic factors should be considered. Several epidemiological features of TC suggest that the disease originates early in life. First, TC incidence rate peaks between 25 and 35 years of age.<sup>6</sup> Second, migrant studies have shown that immigrants keep the risk of TC of their native population.<sup>17</sup> Third, year of birth is a more important risk determinant than calendar year of diagnosis.<sup>18</sup> Fourth, TC incidence is associated with conditions pertaining to pregnancy.<sup>19</sup> Fifth, TC, hypospadias (incomplete closure of the urethral fold), cryptorchidism (undescended testis), and low sperm quality are thought to be symptoms of one underlying entity, the testicular dysgenesis syndrome (TDS), with a common origin in foetal life.<sup>20</sup> In the following, these issues are further described, and a brief outline of the proposed mechanisms being involved in the development of TC is given.

### *Epidemiological features*

Cancer usually takes decades to develop, and cancer types with an early age peak are generally regarded as having been initiated early in life and even *in utero*. Similar inference can be made from migrant studies showing that men moving from a low TC risk area (e.g. Finland) to a high risk area (e.g. Sweden), kept their low risk comparable to those who were still living in Finland.<sup>17</sup>

Several age-period-cohort and frailty modelling studies have independently shown that men born in Sweden, Denmark and Norway during World War II (WWII) have a lower TC incidence than men born in the years before or after WWII.<sup>18,21,22</sup> The underlying mechanisms are still elusive, but most likely relate to the caloric restriction of 5-20% that took place in the Scandinavian countries during the war, since such conditions have been shown to reduce cancer incidence in experimental animals.<sup>23</sup> On the other hand, one cannot exclude an association between TC risk and reduced intake of harmful nutritional components or *vice versa* during WWII.<sup>24</sup> Maternal smoking during pregnancy has been proposed as a causal factor for TC in the offspring.<sup>25</sup> The daily consumption of tobacco

decreased during the war<sup>26</sup> and thus compatible with a reduced risk in the offspring in this period. The overall potential effect of this alteration in maternal smoking, however, was most likely limited, given the low prevalence of female smokers at that time.<sup>26</sup>

### *Testicular dysgenesis syndrome (TDS)*

TDS is thought to have increased in most Western countries over the past decades. These conditions (TC, hypospadias, cryptorchidism, and poor semen quality) share several risk factors and often coincide in affected individuals. The aetiology of the clinical components of TDS syndrome remains unknown in the majority of cases, but is believed to be multi-factorial, involving both genetic and environmental factors, which disturb the gonadal development *in utero*.<sup>20</sup>

The origin of TC (with the exception of spermatocytic seminoma) is believed to be carcinoma *in situ* cells, whose malignant transformation is initiated during the early development from primordial germ cells or gonocytes that fail to end proliferation or undergo proper differentiation.<sup>27,28</sup> The first trimester of pregnancy is therefore considered most critical for the development of TC.

### *Conditions pertaining to pregnancy*

Case-control studies have shown that various maternal factors related to pregnancy are associated with increased risk of TC in the offspring. These factors include infection of the urinary system, retained placenta, and low birth weight.<sup>19,29</sup> In light of the proposed 'oestrogen hypothesis' (see below), a special interest is connected to an elevated risk of TC in boys born in their mothers' first pregnancy. Then the maternal level of bioavailable oestrogen is higher than in subsequent pregnancies due to less sex-hormone binding globulin (SHBG) in nulliparous women. The risk of TC tends to be higher in dizygotic than monozygotic twins, an observation which has also been associated with the higher levels of oestrogen during dizygotic pregnancies. Although, only some of these risk factors have a well-defined relationship with oestrogen, the mere presence of risk factors related to pregnancy underscores the importance of this period.

### *The oestrogen hypothesis*

Over the past decades, there has been concern about a possible adverse trend in male reproduction due to increasing incidence of testicular cancer,<sup>15,16</sup> and possibly also hypospadias and cryptorchidism<sup>30,31</sup> as well as an apparent decrease in semen quality.<sup>32</sup> In 1993, Sharpe and Skakkebak launched the so-called 'oestrogen hypothesis', suggesting that increased exposure to endogenous or exogenous estrogens *in utero* could be a cause of these disorders of the male reproductive tract.<sup>33</sup> Increased exposure to oestrogens early in foetal life may have adverse effect on both Sertoli and

Leydig cells, and thus also on germ cells, and can potentially lead to increased risk of these disorders.

Exposure of pregnant mice to oestrogens has been found to increase the frequency of testicular dysgenesis<sup>34</sup>, cryptorchidism<sup>35</sup>, hypospadias<sup>36</sup> and TC<sup>37</sup> in male offspring; and there is also evidence of impaired Leydig cell development and reduced Sertoli cell numbers, resulting in impaired spermatogenesis.<sup>34</sup> The same associations have been suggested in humans,<sup>38</sup> although they are still under debate.<sup>39</sup> Sons of women who themselves were exposed *in utero* to diethylstilbestrol (DES), may have an elevated risk of TC although the data are not unequivocal.<sup>40</sup>

The most straightforward way by which the foetus could be exposed to high levels of oestrogens, is through increased bioavailability of maternal high oestradiol levels naturally occurring during pregnancy.<sup>39</sup> Bioavailability of oestradiol is mainly regulated by the level of SHBG, whose most important endogenous suppressor is insulin. It has recently been shown that the maternal weight dropped transiently in Norway during WWII, when the population was exposed to energy restriction (15-20%), and by inference, reduced insulin levels.<sup>41</sup> There was a correlation between maternal weight and the risk of TC for those who were born in the study period 1931-55. Given the mechanism outlined above, the insulin level could thus represent a link between increased body mass in most populations during recent decades and the corresponding increased incidence of TC.

Since 1993, the oestrogen hypothesis has been expanded to include also environmental antiandrogens with potential adverse effects on male reproductive health.<sup>20,38</sup> By blocking androgen action, exposure to an antiandrogen may cause changes similar to those associated with oestrogen exposure, and in addition, several environmental oestrogen receptor agonists are also androgen receptor antagonists.<sup>42</sup> Male animals exposed to antiandrogens *in utero* have been found to develop cryptorchidism, hypospadias, infertility, and testis abnormalities similar to those seen in human TDS.<sup>43-45</sup> Thus, according to the latest version of the oestrogen hypothesis, increased exposure to oestrogenic and antiandrogenic endocrine disrupters, or an otherwise change in the androgen-oestrogen balance *in utero*, can lead to disruption of embryonal programming and gonadal development, resulting in more or less grave symptoms of TDS.<sup>20,33,39</sup> It has been suggested that it is the balance between oestrogens and androgens that is important, rather than the relative levels, regarding the risk of TDS.<sup>39</sup>

In summary, although TC is a disease where the evidence in favour of an *in utero* onset is reasonably persuasive, the mechanisms are still elusive. This review has focused mainly on factors acting *in utero*. In addition, there is a genetic component in the aetiology of this cancer form, since a family history of TC in a first-degree relative is a consistent risk factor. Based on recent years' research, there is reason to believe

that studies taking advantage of the concept of TDS, are most likely to provide the most interesting results regarding the aetiology of TC, both in terms of genetic and environmental factors.

## BREAST CANCER (BC)

The median age at diagnosis of BC in Norway before the implementation of mammography screening programmes was 64 years.<sup>46</sup> Studies among young women treated with radiation for Hodgkin disease as well as on BC incidence among atomic bomb survivors strongly indicate the importance of early life exposure for BC development.<sup>47</sup> In 1990, Trichopoulos proposed that BC might originate already *in utero*.<sup>48</sup> Both previous and recent studies have given support to this statement. First, migrant studies indicate that the age at migration is related to the acquisition of BC risk from the host country. Second, BC incidence is associated with conditions pertaining to pregnancy, such as pre-eclampsia. Third, BC is associated with birth weight. Fourth, animal studies support the importance of conditions *in utero*.

### *Migrant studies*

Migrant studies have evidenced that adaptation of BC rates in the first generation depends on age at migration. Adaptation is more evident in the second generation migrants. Particularly if the women move at very young age, they adopt the BC rates in the host country.<sup>49,50</sup> This indicates a clear effect of factors acting early in life other than genetical susceptibility in BC aetiology.

### *Conditions pertaining to pregnancy*

There is some evidence that women who are firstborn have an increased risk of BC, and a higher risk is seen among dizygotic than monozygotic twins.<sup>51</sup> The supposed mechanisms are associated with higher oestrogen levels as discussed for TC above. Studies conducted in Sweden with information abstracted from patients' medical records, indicate that the offspring of mothers who had pre-eclampsia, have a substantially reduced BC risk later in life.<sup>14</sup> A study by Sanderson et al.<sup>52</sup> supported this observation based on self-reports from the mothers. A large study conducted in Norway, found a 20% decreased pre- and post-menopausal BC risk among daughters of women with pre-eclampsia and or hypertension during pregnancy. These results were consistent both in term and pre-term deliveries, and across different birth weights.<sup>53</sup> The mechanism involved may include lower levels of foetal oestrogen exposure, which characterises pregnancies with pre-eclampsia. There is some evidence that the anti-oestrogenic effect associated with pre-eclampsia may be mediated through high levels of alpha-foetoprotein rather than low levels of oestradiol.<sup>54</sup>

Maternal age at time of birth has been associated

with BC risk in the daughters in some studies.<sup>51</sup> Oestrogen levels may be higher in older pregnant women, although results on hormonal levels relative to age have been inconsistent. Some further studies are warranted to clarify this area.

Length of gestation has been inconsistently associated with a higher risk of BC.<sup>52,55-58</sup> We could not identify epidemiological studies in humans suggesting clear effects of maternal diet and BC risk in the daughters. Findings in animal studies, however, suggest that increased exposure to oestradiol in foetal life and adolescence, significantly affects BC risk,<sup>59</sup> indicating that the time of exposure of the breast to oestradiol is of importance for carcinogenesis in this organ. Elevated birth weight due to obesity induced in the mothers has also been shown to affect both the incidence and the number of breast tumours per animal. Maternal exposure to a high fat diet and alcohol, increases pregnancy oestrogen levels, and moderate alcohol intake during pregnancy increases BC risk in the offspring.<sup>60</sup> Studies in mice have demonstrated that BC risk can be manipulated by diet during pregnancy and adolescence. Thus, dietary factors during pregnancy associated with a reduced BC risk in the offspring, were whole wheat diet (very rich in fibre), and low fat fish oil. The corresponding dietary factors increasing BC risk in the offspring were genistein, alcohol, fat diet, including high fat fish oil, and fibre from flaxid. Interestingly, while a pregnancy diet rich in genistein reduced risk of BC, a similar diet administered during puberty increase risk,<sup>61</sup> indicating that the timing of dietary exposure may produce different effects in terms of BC risk.

### ***Anthropometric measurements at birth***

Most studies looking at early life events in relation to BC risk, have been dealing with birth weight, as a proxy for foetal growth rate and gestational duration, in addition to possibly other as yet unidentified foetal exposures. Birth weight is also influenced by genetical factors, maternal pre-pregnancy weight, weight gain during pregnancy, maternal diet during pregnancy, and pregnancy hormone levels (insulin-like growth factor 1 and 2, oestrogen, and leptin, among others). There are at least 20 published studies on birth weight as determinant of BC risk, most of them<sup>14,53,57,58,62-74</sup> indicating that birth weight is positively associated with BC risk. While the evidence of a positive association between birth weight and premenopausal BC is quite convincing, the data for post-menopausal BC are less consistent.<sup>51</sup>

Besides birth weight, birth length is of interest. McCormack et al.<sup>68</sup> found that the effect of birth weight disappeared after adjustment for birth length or head circumference, whereas the effects of birth length and head circumference remained significant after adjustment for birth weight. Few studies have been published in this area, and more information is warranted. In a Norwegian study, the odds ratio for women who

were in the highest quartile of birth length was increased compared with those being in the lowest quartile.<sup>64</sup>

Other childhood and adolescent characteristics such as high stature in adolescence, and peak growth at an early age have been convincingly associated with BC risk, and they seem to interact with birth weight.<sup>63</sup>

## **OTHER TYPES OF CANCER**

Anthropometric measurements at birth have been linked to several types of cancer. These studies have been performed as a result of the findings in the BC studies, but also because birth weight and length are the only quality data from the intrauterine period available for studies of adult cancer. The other focus on exposures during intrauterine life is rooted in the difficulties in obtaining specific exposure data far back in time. These difficulties imply that studies can mainly be conducted for childhood cancer. Thus, care must be taken when making inferences from the results, due to the differences that often exist between cancer in childhood and adulthood, which may reduce the general applicability of the results. The childhood cancer studies are usually retrospective and hence highly vulnerable for selection bias. In addition, it is difficult to state if an exposure has been specific to the *in utero* period only, and the studies often include a small number of cases. In the following, a short summary of the birth weight studies and the childhood cancer studies are presented.

### ***Birth weight***

Eight studies examining the association between birth length and weight and prostate cancer, have revealed inconsistent results. In the five studies that did not show any association,<sup>62,75-78</sup> the number of cases varied between 192 and 834. Nilsen et al. found an association with birth length and metastatic prostate cancer, but not for all stages of prostate cancer combined.<sup>79</sup> Tiblin et al. found a significant association with high birth weight, but the study was based on only 21 cases.<sup>80</sup> In a Danish study<sup>81</sup>, a significant positive association was seen among those with birth weight more than 3500 g, but the study comprised only 56 individuals.

Bergstrom et al. found a weak association with kidney cancer when comparing those with birth weight above 3500 g with 3000-3499 g, but only in males.<sup>82</sup> Ahlgren et al. found a tendency to increased incidence by increasing birth weight, both for kidney and bladder cancer.<sup>81</sup> The association was found only in birth weight groups below 3500 g for kidney cancer and above 3500 g for bladder cancer. In a recent study, however, no association was found between birth weight and malignant neoplasm in the urinary system.<sup>62</sup>

Several studies have shown an elevated risk of Wilms' tumour among children with a high birth

weight, and it is suggested that the association is restricted mainly to children aged less than 2 years at diagnosis. The largest study with 1800 cases pinpointed the heterogeneity in the pathogenesis of Wilms' tumour, and that the strength of the association was different for the various sub-types.<sup>83</sup>

Sandhu et al. suggested a J-shaped relation between self-reported birth weight and colorectal cancer.<sup>84</sup> Babies born with macrosomia appear to have the greatest risk. However, the study was based on 52 cases only. A larger study<sup>62</sup> showed a 16% elevated risk per one standard deviation increase in birth weight while a third study<sup>81</sup> found no association between birth weight and colorectal cancer.

McCormack et al. found a reduced risk by increasing birth weight among 112 cases of endometrial cancer,<sup>62</sup> whereas Ahlgren et al. could not demonstrate any association neither for endometrial, cervix nor ovary cancer.<sup>81</sup> Both these studies<sup>81,62</sup> demonstrated an increased (but non-significant) risk of pancreatic cancer by increasing birth weight. Furthermore, in the Danish study a significant positive association was seen between birth weight and lung cancer,<sup>81</sup> while a positive trend of borderline significance for cancer in the respiratory system was observed in the study by McCormack et al.<sup>62</sup>

The results for malignant melanoma have been inconsistent.<sup>62,81</sup> McCormack et al. found a significant positive association between birth weight and cancer in the lymphatic and haematopoietic tissue in adult persons, and a similar tendency was seen for multiple myeloma and Non-Hodgkin lymphoma. A meta-analysis of more than 10 000 children concluded with an increased risk of acute lymphoblastic leukaemia for those with a birth weight of more than 4000 g compared with weight less than 4000 g.<sup>85</sup> These results have been confirmed in a recent Nordic study.<sup>86</sup>

Neither McCormack et al.<sup>62</sup> nor Ahlgren et al.<sup>81</sup> could find any association between birth weight and cancer in the brain or the nervous system in adult persons. However, a relationship has been shown between high birth weight (more than 4000 g) and the incidence of astrocytoma.<sup>87</sup>

A significant positive association between birth weight and all types of cancer combined is seen for males and for females under age of 50 years.<sup>62</sup> The demonstrated association found for BC in premenopausal women dominated the association for cancer combined for women under 50 years. In the Danish study, a positive association between birth weight and all types of cancer combined was seen both for men and women.<sup>81</sup>

#### **Other exposures during intrauterine life**

In 1999, Little<sup>87</sup> published an extensive review of childhood cancer, the most frequent types being leukaemia, brain tumours and lymphoma. According to the review, exposure to diagnostic X-rays *in utero* is

associated with leukaemia, whereas paternal occupational exposure to solvents, paternal smoking and maternal alcohol consumption during pregnancy are classified as *associated with some degree of consistency* with leukaemia. For lymphoma, no factor *in utero* has been found to be *consistently associated*. For brain tumours, exposure to diagnostic X-rays *in utero* is classified as *associated*. Maternal consumption of cured meats during index pregnancy, maternal use of vitamin supplements during early pregnancy and high birth weight (astrocytoma) have been classified as *associated with some degree of consistency*.<sup>87</sup>

Among the less frequent types of childhood cancer, maternal use of sex hormones before or during pregnancy has been *associated with some degree of consistency* with neuroblastoma. Regarding Wilms' tumour, a similar classification exists for high birth weight and paternal employment in occupations potentially involving exposure to metals.<sup>87</sup>

#### **COMMENTS**

The overwhelming problem in testing the *in utero* hypothesis is the difficulty of getting relevant exposure data from the *in utero* period. Birth weight and length have been registered carefully for a long time, and that is likely the main reason for all the studies carried out on birth weight and cancer later in life. However, a feeling remains that the proverbial "*lamppost has been successfully moved to the place where the keys were lost*", applies. On the other hand, an association between birth weight and a cancer form indicates that something related to the birth weight is a potential causal factor for the cancer form in question.

So far, the results have indicated that the hormonal conditions during pregnancy may be of importance. Another issue is whether birth weight can be related to number of cells at risk in the organ. The old multistage models assume that a set of tissue cells serve as the basis for all the events that take place before a cancer is detected. The risk depends on the number of cells in this set. It has been calculated that about 42 rounds of cell divisions in the fertilised human ovum occur before birth and only a further five division after birth.<sup>88</sup> It is rather well documented that adult height is a risk factor for breast<sup>89</sup> and colo-rectal cancer<sup>90</sup>, but also for malignant melanoma<sup>91</sup>, and uterine corpus cancer<sup>92</sup>. These observations have been linked to the number of cell under risk for acquiring cancer.<sup>82,93,94</sup> Recently, Ballen et al.<sup>95</sup> have shown that foetal growth reflects the number of primitive proliferating cells in umbilical cord blood which may be an indication of the susceptibility to cancer.<sup>96</sup>

Knowledge about specific exposures *in utero* and cancer is almost absent. However, the association between radiation exposure *in utero* and cancer<sup>97</sup> and between use of DES<sup>40</sup> and cancer, may illustrate the need for more information and hopefully from pros-

pective studies. For most types of cancer, specific exposures in adult life are better documented as risk factors for cancer. The frailty model for TC<sup>98</sup> indicates that the proportion of frail men increases over birth cohorts. This could happen if the frailty arises through a gene-environment interaction during intrauterine life. Different adult exposures may modify the disease process among the frail persons, providing an array of variation in time delay until the cancer is diagnosed. Some frail individuals may even die from other causes before this occurs. While limited knowledge exists about adult risk factors for TC, the situation is somewhat different for BC and some other types of cancer. In lung cancer development, frailty most likely play a role, but smoking habits are of decisive importance.

The foetal life is critical for the development of the different organs and conditions *in utero* seem to influence not only cancer, but also other types of diseases later in life. This calls for increased focus on pregnancy as a potential disease preventive phase of life.

However, as of today, we should apply with care the limited knowledge about exposures *in utero* in cancer prevention.

A problem in epidemiology is the huge number of association studies carried out in adult populations to examine the importance of different environmental or lifestyle factors for cancer incidence. Mainly factors measured close to the time of diagnosis are considered. Individual hereditary conditions or acquired susceptibility for cancer *in utero* make an interesting background for reviewing and interpreting previously conducted studies and in the planning of new studies. The accumulating evidence of the conditions *in utero* being relevant for the origin of some cancer forms, ought to stimulate experimental studies aimed at testing specific hypotheses to a larger extent than what has been done so far. However, it has been claimed that it is too limited to focus solely on the situation *in utero*, and that conditions in early life should be included, but this was beyond the scope of this review.

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