

Article

Meta-analysis of cancer triploidy: Whole-genome rearrangements in male human tumours are characterised by XXY karyotypes

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Abstract: Triploidy in cancer is associated with poor prognosis but its origins remain unclear. Here, based on frequent X-chromosome doubling in male tumours we attempted to differentiate between a random chromosomal origin and whole-genome origin of cancer triploidy. *In silico* meta-analysis was performed on 15 male malignant and 5 benign tumour cohorts (2928 karyotypes) extracted from the Mitelman Database, comparing their modal chromosome numbers (ploidy) and combinations of sex chromosomes. Karyotype heterogeneity with a distinct near-triploid fraction was observed in all malignant tumour types, especially high in seminoma. For all tumour types, X-chromosome doubling, dominantly presented by XXY, strongly correlated with the near-triploid state ($r \approx 0.9$, $p < 0.001$), negatively correlated with near-diploidy, and did not correlate with near-tetraploidy. The proportion of XX,-Y near-triploid karyotypes was variably increased in somatic tumours. A smaller near-triploid component with a doubled X-chromosome was also present in 3 of 5 benign tumour types, especially notable in colon adenoma. We conclude that doubling of the maternal genome followed by fusion with a paternal genome (similar to digyny) is likely responsible for the observed whole genome triploidy and may be causative for cancer initiation. The Y-chromosome may subsequently be lost due to secondary chromosome instability processes.

Keywords: cancer near-triploidy, male tumours, karyotype meta-analysis, XXY, whole genome rearrangements, digyny.

1. Introduction

Aneuploidy (an abnormal number of chromosomes) is a well-known hallmark of malignant tumours, generally associated with a poor prognosis for patients [1,2]. In aneuploid solid tumours, a near-triploid karyotype is often associated with increased aggressiveness and resistance to chemotherapy [3,4]. It is widely accepted that aneuploidy in cancers originates from whole diploid genome doubling (tetraploidy), which then randomly gains and loses chromosomes through a series of aberrant mitoses before settling as a relatively stable near-triploid karyotype by clonal selection of the fittest mutant [4–6]. Hypodiploidy (near-haploidy) followed by duplication to triploidy was revealed by single-cell sequencing in the evolution of triple negative breast cancer [7]. Still, neither this data, nor the “trade-off” hypothesis of clonal selection of the fittest clones arising through random chromosome and gene mutations [1,2] exhaustively explains the „cancer aneuploidy paradox” - the ability of the tumour to undergo unlimited growth in spite of the accumulation of neutral and harmful stochastic mutations would ultimately stop proliferation and cause cell death [8]. Earlier, we postulated a “cancer cell life cycle”, composed of two reciprocal parts: the mitotic cycle, and the reproductive ploidy cycle which is capable of counteracting

aneuploidy and supporting immortality [9–11]. The existence of reproductive ploidy cycle is supported by expression of multiple meiotic genes associated with reversible polyploidy and the blastomere-like conversion of polyploid multinucleated tumour cells which have been reported in female and male tumours, intact and particularly genotoxically stressed [12–19]. Ploidy cycles involving somatic meiosis would double and half the number of the genomes [20]. The preferred triploid state (around 69 chromosomes) of cancer observed in many established tumours and *in vivo* challenges this concept. Therefore, we paid attention to the fact that among the numerical sex chromosome aberrations in male patients, the assertive acquisition of an extra X chromosome and loss of the Y chromosome have been noticed in several tumour types [21–27], particularly in association with triploidy in the male germ cell tumour seminoma [28].

Here, we decided to use the advantage of the presence of two different sex chromosomes, X and Y, in a normal diploid male karyotype, in order to attempt the differentiation between two mechanisms in the origin of tumour near-triploidy - the chromosomal aberrations and the whole-genome change. For this purpose, we performed an *in silico* meta-analysis of the male tumour karyotypes deposited in the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer.

2. Materials and Methods

The karyotypes from 15 male malignant solid tumour types (untreated and presented in the >50 number of cases), epithelial and mesenchymal, somatic and germinative, and karyotypes from 5 benign tumour types were obtained from the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer [29]. None of the male patient karyotypes was affected with congenital sex chromosome aberrations such as Klinefelter syndrome. The types of tumours and the number of patient karyotypes for each of them are presented in Table.1.

The tumour Nomenclature used was based on the International Classification of Diseases for Oncology (ICD-O), the Systematized Nomenclature of Medicine (SNOMED), and the WHO Classification of Tumours of Soft Tissue and Bone - the same sources as the Mitelman database's nomenclature. Seminoma was the germ cell tumour. Among somatic tumours, the lung carcinoma cohort included a total of 5 lung tumour types (squamous cell carcinoma, adenosquamous carcinoma, adenocarcinoma, undifferentiated large cell carcinoma, and small cell carcinoma), united from the evidence that both bronchoepithelial and neuroendocrine lung stem cells likely have one common precursor [30]. The gastric carcinoma cohort was comprised of adenocarcinoma and undifferentiated carcinoma. These cases were not sorted by stages of the malignant process in the Mitelman database. Only monoclonal karyotypes comprising in total 2928 tumour cases were collected, filtering out the cases with polyclonal karyotypes, the cases where several samples were obtained from one patient, the cases with fragmented sex chromosomes or incomplete karyotypes. Using the data analysis tools of the numpy [31], pandas [32] and scipy [33] Python libraries, statistical analysis of the available data was performed to determine the relationship between modal chromosome numbers and different sex chromosome karyotypes were analysed.

The 2013 edition of the International System for Human Cytogenetic Nomenclature (ISCN) defines near-triploidy as a modal chromosome number that falls in the 58-80 range [34]. In this study, however, the boundaries of what constitutes near-triploidy were narrowed further in order to improve the precision of the data analysis by lessening stochastic aneuploidy "noise", with a wider range spanning 62-76 chromosomes, and a narrower range spanning 66 to 72 chromosomes.

Table 1. The analyzed tumour types, the number of karyotypes per cohort, the percent share of near-triploidy (in the wide range 62-76 chromosomes), and the percent share of sex chromosome configurations containing a doubled X-chromosome.

No	Malignant tumour type	Number of karyotypes	% of near-triploidy (62-76)	XXY %	XX,-Y %	(XY,+X)+ (X,-Y,+X) %	XXY,+Y %
1	Seminoma	78	42.31	47.44	3.85	5.13	10.26
2	Osteosarcoma	61	27.87	24.59	3.28	0.00	6.56
3	Lung carcinoma	237	27.00	8.02	9.70	2.53	2.53
4	Gastric carcinoma	74	20.27	10.81	5.41	6.76	1.35
5	Head and neck squamous cell carcinoma	191	16.75	5.76	8.90	0.52	1.57
6	Colon adenocarcinoma	98	16.33	12.24	6.12	10.20	6.12
7	Transitional cell carcinoma	104	13.46	4.81	3.85	1.92	1.92
8	Chondrosarcoma	85	11.76	4.71	3.53	3.53	0.00
9	Malignant melanoma	134	10.45	5.22	3.73	2.24	2.24
10	Glioblastoma	215	10.23	7.44	1.40	0.00	1.40
11	Renal carcinoma	577	7.11	3.81	4.68	1.04	1.21
12	Mesothelioma	72	6.94	5.56	2.78	0.00	2.78
13	Rhabdomyosarcoma	92	6.52	3.26	1.09	3.26	0.00
14	Ewing sarcoma	228	3.51	3.95	0.00	3.51	0.88
15	Liposarcoma	147	3.40	1.36	1.36	0.00	0.00
	Benign tumour type						
16	Colon adenoma	62	11.29	11.29	4.84	0.00	0.00
17	Astrocytoma	59	6.78	1.69	1.69	1.69	1.69
18	Lipoma	235	0.85	0.85	0.00	0.00	0.43
19	Renal adenoma and oncocytoma	48	0.00	0.00	2.08	0.00	0.00
20	Salivary gland adenoma	131	0.00	0.00	0.76	0.00	0.00

3. Results

3.1. Analysis of the histograms of the modal chromosome numbers in 15 cohorts of malignant tumours

In all examined malignant tumour types, listed in Table 1, the aneuploid karyotypes were present. The summary histograms of the modal chromosome numbers of each cohort are presented on Fig.1.

It is seen that they include near-diploid karyotypes, near-triploid karyotypes, a degree of tetraploidy and in many cases also hyper-tetraploid karyotypes. The near-triploid karyotypes were present in all malignant tumour types. Their percentual share for malignant tumour types 1-15 is presented in Table 1 in the descending order. In particular, the high proportion of near-triploidy (42%) was observed for the germ tumour, seminoma. In 14 examined somatic malignant tumour types, both epithelial and mesenchymal, the near-diploid karyotypes were dominating, while the proportion of near-triploid ones was less pronounced than in seminoma, albeit in a varying degree (Table 1, Fig.1). Osteosarcoma was a leader in triploidy (28%). Lung carcinoma also displayed a high proportion of near-triploid karyotypes (27%), other somatic tumours showed lower values.

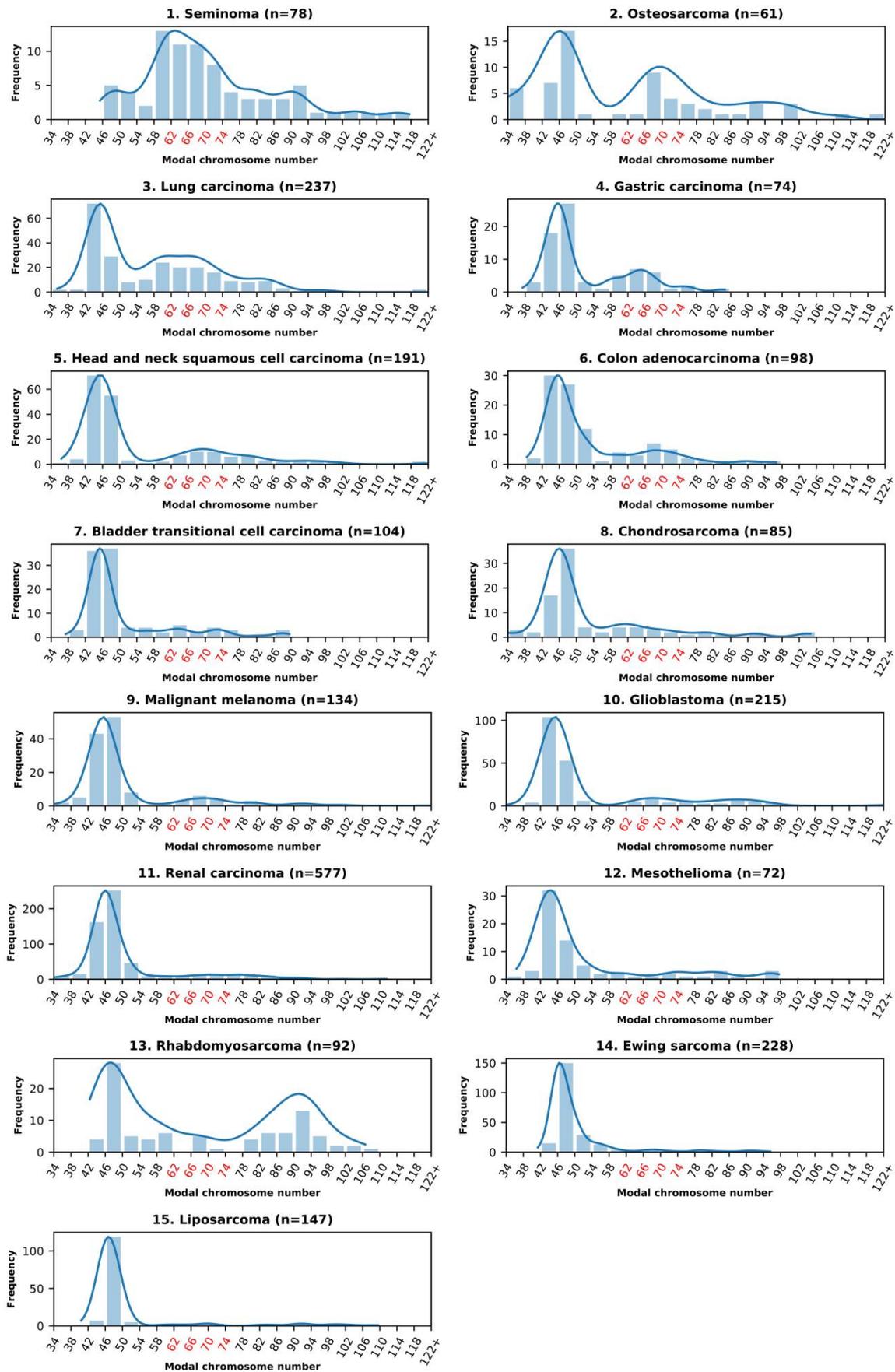


Figure 1. The modal chromosome number frequency histograms of 15 malignant tumour cohorts, numbered as listed in Table 1. The chromosome numbers within the (arbitrarily chosen) wide range of near-triploidy (62-76 chromosomes) are marked red.

3.2. Analysis of the sex chromosome sets with doubled X-chromosome in each malignant tumour cohort in relation to ploidy of their karyotypes.

We also analysed the sex chromosome sets with doubled X-chromosomes, which are presented and percent proportions for each malignant tumour cohort in Table 1. It can be seen that configuration XXY is dominating in seminoma and also mostly dominating in 12 of 14 somatic malignant tumours. However the proportion of XX,-Y set is larger in them than in seminoma, while in head and neck (HN) squamous cell carcinoma XX,-Y is prevailing over XXY. Other karyotypes with doubled X (XY,+X) + (X,-Y,+X) were in minority, with the exception of colon adenocarcinoma, where their proportion was comparatively high. Some of the (largely near-triploid) XXY karyotypes were also revealed to possess an extra Y chromosome (especially evident in seminoma, osteosarcoma and colon adenocarcinoma); their percentual share is presented in the last column of Table 1.

Further, we compared the relationship of the karyotypes with doubled X-chromosome with ploidy range of the modal chromosome numbers. The results of this comparative statistical analysis are shown on Fig.2 and 3.

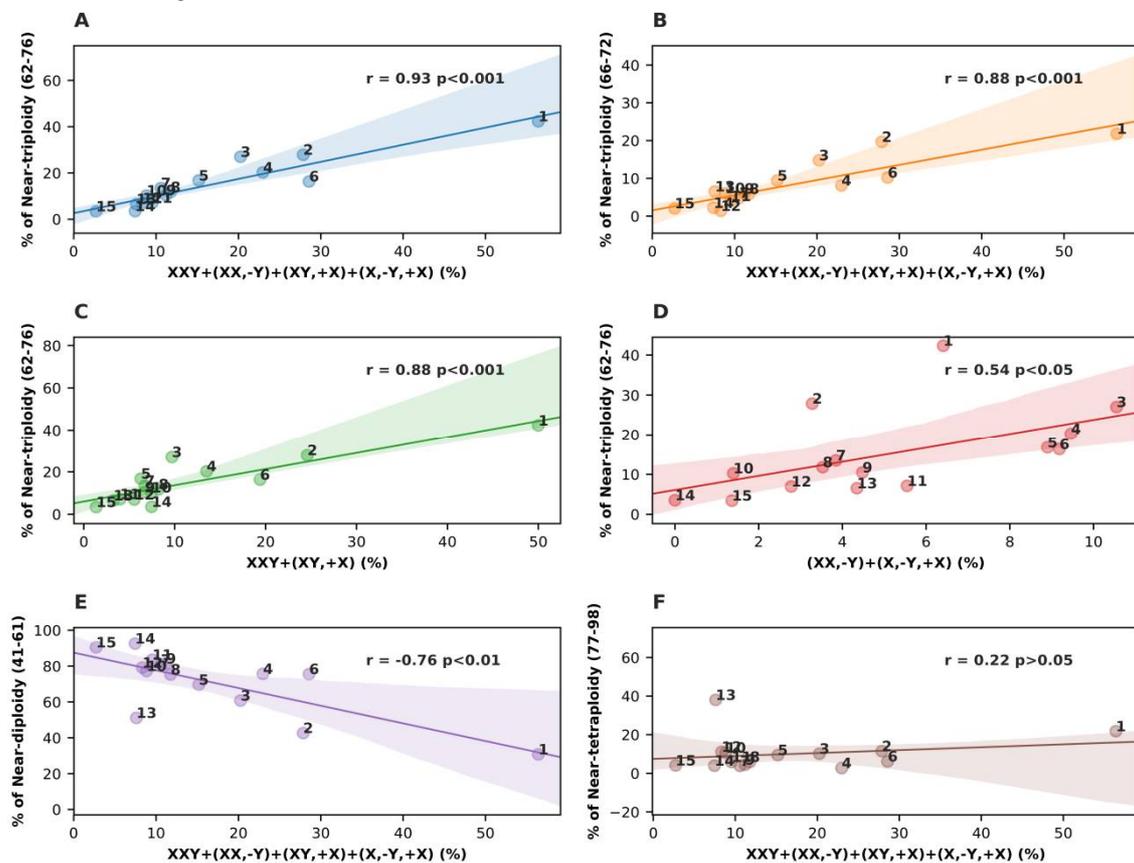


Figure 2. Results of the Pearson correlation analysis for all 15 patient karyotype cohorts of malignant tumours evaluating the relationship between karyotypes containing doubled X-chromosomes (both with and without an Y chromosome), and ploidy in different chromosome ranges: (A) all karyotypes with doubled X in relation to triploidy in the wide range (62-76 chromosomes); (B) all karyotypes with doubled X in relation to triploidy in the narrow range (66-72 chromosomes); (C) double X-karyotypes with an Y chromosome in relation to the wide range of near-triploidy; (D) double X-karyotypes lacking an Y chromosome in relation to the wide range of near-triploidy; (E) Karyotypes with doubled X related to near-diploidy (41-61 chromosomes); (F) karyotypes with doubled X related to near-tetraploidy (77-98 chromosomes).

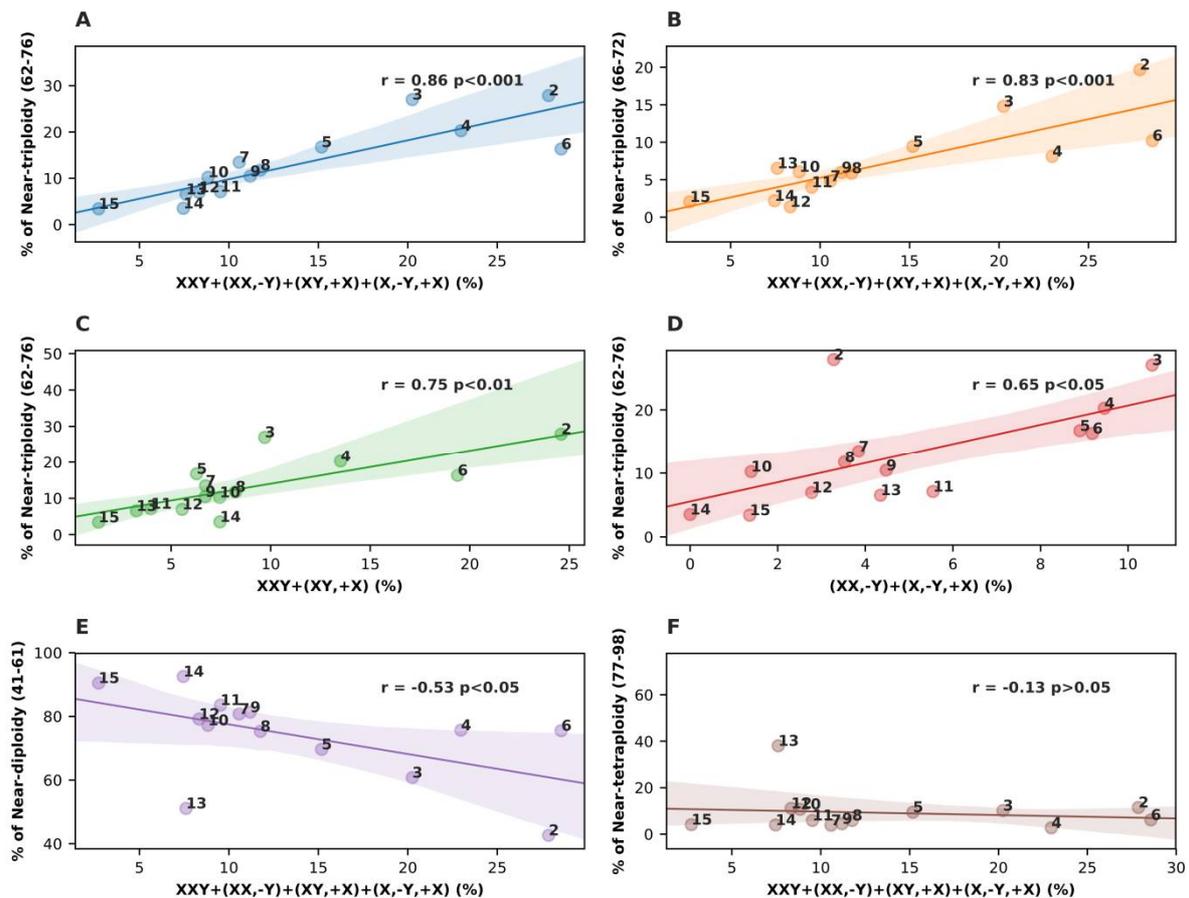


Figure 3. Results of the Pearson correlation analysis for 14 cohorts of only somatic malignant tumours evaluating the relationship between karyotypes containing doubled X-chromosomes (both with and without an Y chromosome), and ploidy in different chromosome ranges: (A) all karyotypes with doubled X in relation to triploidy in the wide range (62-76 chromosomes); (B) all karyotypes with doubled X in relation to triploidy in the narrow range (66-72 chromosomes); (C) double X-karyotypes with an Y chromosome in relation to the wide range of near-triploidy; (D) double X-karyotypes lacking an Y chromosome in relation to the wide range of near-triploidy; (E) karyotypes with doubled X related to near-diploidy (41-61 chromosomes); (F) karyotypes with doubled X related to near-tetraploidy (77-98 chromosomes).

Strikingly, in spite of the many-fold difference in proportions of the near-triploid karyotypes among 15 malignant tumour types, all together provided a very high Pearson correlation with the sex chromosome karyotypes possessing double-X-chromosome ($r=0.93$, $p<0.001$ and $r=0.88$, $p<0.001$) in the wide and narrow range of near-triploidy, correspondingly (Fig.2A and 2B). For 14 somatic malignant tumours only, as presented on Fig.3A and 3B, this correlation was also high ($r=0.86$, $p<0.001$ and $r=0.83$, $p<0.001$), in the wide and narrow range of near-triploidy, correspondingly. The sex chromosome set XXY, which was dominating ensured most of this positive correlation, which was higher with seminoma (compare Fig.2C and 3C). On the contrary, the sets with double-X but lost Y-chromosome had a lower positive correlation with near-triploidy when seminoma was present ($r=0.54$, $p<0.05$) and increased ($r=0.65$, $p<0.05$) when only somatic malignant tumours were included (compare Fig.2D and 3D), as due to the larger share of this subfraction in them (Table 1). However, as shown in Fig.2E and 3E, all chromosome sets with doubled X-chromosomes for 15 malignant tumours had a statistically significant negative correlation with the hypo-hyper-diploid

range of the modal chromosome number (41-61 chromosomes): with seminoma ($r=-0.76$, $p<0.01$) and without it ($r=-0.53$, $p<0.05$). Fig.2F and 3F show that the double-X-chromosome sets did not significantly correlate with near-tetraploidy (77-98 chromosomes).

3.3. Analysis of all sex chromosome configurations in relation to near-triploidy in malignant tumours.

The relationship between near-triploidy in the wide range (62-76) and all sex chromosome sets is presented in bars for all malignant tumours on Fig.4. Besides the already discussed issues of prevailing association of doubled X-chromosome karyotypes with near-triploidy, Fig.4 also reveals that a small part of XY karyotypes and X,-Y karyotypes are also near-triploid, in particular, this is pronounced in lung carcinoma. Likely, it is associated with the chromosome instability processes. Contrary to the karyotypes with doubled X-chromosome, the compositions of sex chromosomes with doubled Y and one or absent X (XYY or YY) were rare (and therefore not presented): 10 of 16 tumour types (seminoma, osteosarcoma, lung carcinoma, colon adenocarcinoma, gastric carcinoma, bladder transitional cell carcinoma, liposarcoma, chondrosarcoma, Ewing sarcoma and glioblastoma) were lacking them. Only one near-triploid XYY - karyotype was found in the entire analyzed dataset, in rhabdomyosarcoma.

3.4. Benign tumours: Study of the doubled X-chromosome karyotypes and near-triploidy.

As triploidy in association with X-chromosome doubling was found in all malignant tumours we were interested if these features could be also found in premalignant somatic lesions. For that four available pairs of sufficiently large tumour cohorts were compared: astrocytoma versus glioblastoma, colon adenoma versus adenocarcinoma, kidney adenoma and oncocytoma versus adenocarcinoma, lipoma versus liposarcoma and salivary gland adenoma added as the fifth cohort. The results are presented in Table 1 (Nr 16-20) and Fig.5.

In colon adenoma and adenocarcinoma, the proportion of doubled-X sets and relevant near-triploidy was rather similarly high, however, triploidy in adenoma was lower than in colon adenocarcinoma (11% vs. 16%, correspondingly). More detailed analysis of colon adenoma shows that 11 % of near-triploid karyotypes were clearly XXY and in addition, ~5% were XX,-Y (Table 1, Fig.5). Astrocytoma had at least twice lower both values (doubled-X and near-triploidy) as compared with glioblastoma, the same with lipoma and liposarcoma (although both were in the low range of the two values). Kidney adenoma was 4-fold poorer with doubled-X karyotypes than its malignant counterpart (2 % vs. 8%) and did not show triploidy. Salivary gland adenoma also did not display triploidy and extremely low doubled-X value (0.76%).

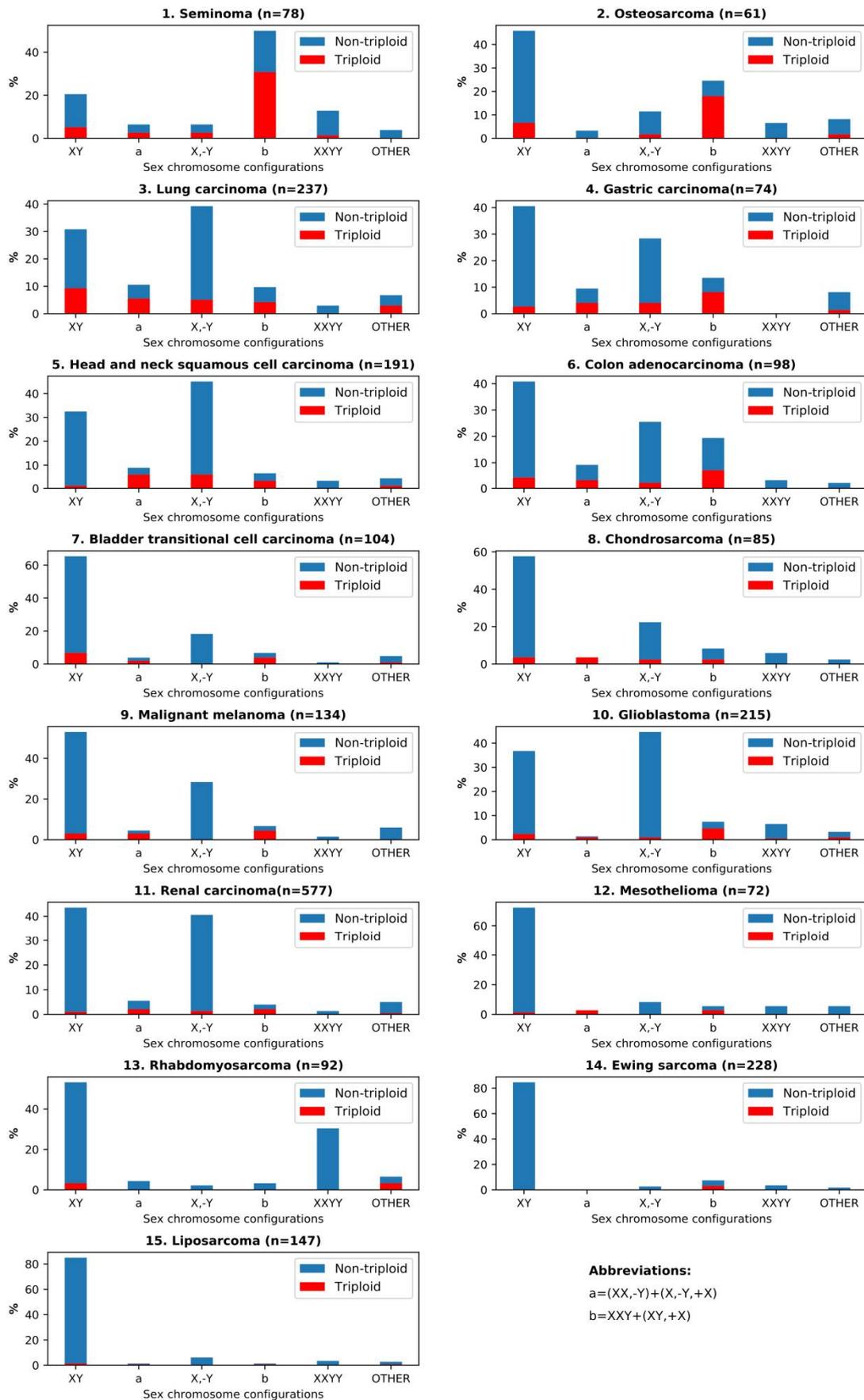


Figure 4. The percent shares of different sex chromosome configurations and their respective percent shares of near-triploidy (62-76 chromosomes) for all malignant tumour cohorts numbered as listed in Table 1.

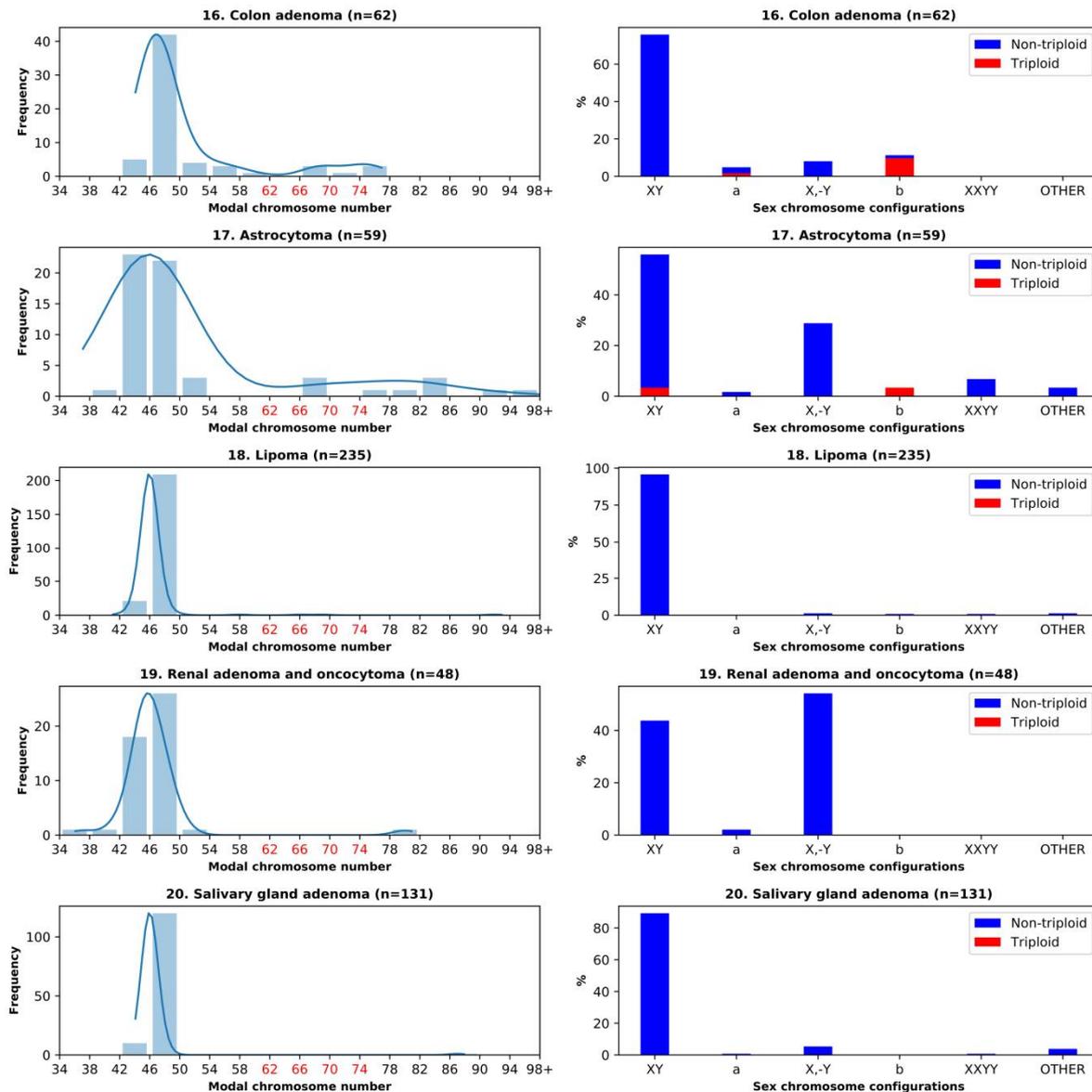


Figure 5. Left column – the histograms of the modal chromosome numbers, with near-triploidy wide range marked red. Right column - the corresponding percent shares of different sex chromosome configurations with doubled X-chromosomes and their respective percent shares of near-triploidy (62-76 chromosomes) for 5 benign tumour cohorts. Designations (a, b) in the right column - **a**: doubled-X karyotypes lacking a Y chromosome (XX,-Y and X,-Y,+X); **b**: doubled-X karyotypes with a Y chromosome (XXY and XY,+X).

4. Discussion

In this study, we hypothesised that tumour near-triploidy may originate primarily from the whole-genome rearrangement and attempted to differentiate it from aneuploidy resulting from chromosomal aberrations. As a method, we chose to analyse the sets of sex chromosomes in their relation to modal chromosome numbers in karyotypes. Through all analysed material representing 20 types of epithelial and mesenchymal, somatic and germ male tumour karyotypes we found several regularities: (1) all karyotypes with doubled X-chromosome sets are tightly associated with the near-triploidy but not with near-diploidy or tetraploidy; (2) The proportion of such doubled-X near-triploid karyotypes dominates in germ tumour, seminoma, it is modest and variable in

somatic tumours, and typically the lowest in the benign counterparts (except for colon adenoma). (3) Nevertheless, double X-chromosome karyotype pervasively linked to near-triploidy is present in all of them, malignant and benign, germline and somatic, carcinomas and sarcomas (except for extremely benign salivary gland adenoma and the combined cohort of two benign renal tumours (adenoma and oncocytoma), which are merely diploid); (4) The XXY configuration is generally dominating, which should be expected for the whole genome triploidy. However, other configurations with doubled X show loss of Y (XX,-Y), and configurations ((XY,+X) + (X,-Y,+X)) presume also a loss of Y and/or some autosomes. The general lessening proportions of altered in relation to XXY karyotypes seen in Table 1 suggests that the whole genome XXY triploidy is the first step in creating triploidy, which is often followed by the second step, loss of Y and also some other chromosomes, caused by the chromosome instability. It follows literary that the triploidy of malignant tumours is initiated by the fusion of two maternal genomes with one paternal genome.

The tight association of near-triploidy with X-chromosome doubling found in all malignant tumour cohorts, however proportionally dominating in seminoma, suggests that this process, both in somatic and germ tumours, may have a germ-like nature. It thus may be primarily related to whole-genome rearrangements of a pseudo-meiotic origin. Judging by the data on benign tumours (mostly colon adenoma), this germinative mechanism could likely be involved in the origin of malignancy (however, this claim still requires further backup research due to the small number of benign tumour samples available in the database). The support for this hypothesis can be found in the study by Castedo et al [28], who revealed the prevalence of triploidy in classic seminoma, including clinical 1st stage and cancer in situ. In turn, the excess X-chromosomes reported in seminomas have also been shown to be activated [35]. The whole genome changes favoured in seminoma are most likely associated with meiosis and potential parthenogenesis, which take the oogenic route, thus explaining maternal genome doubling and the insignificance of the Y chromosome for it. Moreover, the frequent loss of the small, gene-poor Y-chromosome is known to occur in many cancers [36]. Thus, Y chromosome loss is a frequent early event in urothelial bladder cancer, while the loss of the Y chromosome is a frequent chromosomal imbalance in pancreatic cancer and allows differentiation with chronic pancreatitis. Mammalian male germ cells have been observed to possess the ability to convert into oocytes and give rise to parthenogenetic embryos if grown outside the testicles. E.g. for mouse, the loss of Y-chromosome was observed on conversion of spermatogenic epithelium into oocytes and parthenotes by in vitro conditions [37]. The development of blastula from male embryonic stem cells [38] and blastula-like cells in irradiated male lymphoblastoma [15] have been also reported. The pervasively doubled X chromosome may be due to stable meiotic cohesion of sister chromatids in meiosis I also found in pseudo-meiosis of the somatic tumour cells [11,14,15]. All this can serve as an explanation for the identified tight association of the doubled X-chromosome with whole genome rearrangements, which thus could be primarily associated with tumour cell reprogramming to the pseudo-meiotic pathway.

The chromosomes of cancer karyotypes in the Mitelman database are more or less numerically and structurally rearranged [4,6]. Therefore, an aspect of the chromosome instability with random structural chromosome aberrations, individual chromosome gain and loss, and selection of the genetically and proteomic fittest clones, without a doubt, contributes in tumour progression [6]. In fact, we were able to reveal both processes, the whole genome reprogrammed rearrangement and random chromosome aberrations, overlapping in the near-triploidy range. We believe that could provide the data for their differentiation. Often the loss of the Y-chromosome and larger chromosome instability manifested by the karyotypes departing from the initial ~69 XXY, appear to be secondary and more typical for full-blown somatic tumours. If we turn to our hypothesis of the

cancer cell life cycle composed reciprocally from the mitotic and reproductive ploidy cycle [9,11], this difference between germ and somatic tumours causes no surprise: the developed somatic tumours (unless genotoxically stressed) spend more of their life-span in the mutagenic mitotic cycle than in reciprocal germinative ploidy cycle, which is able to more effectively repair the DNA damage [9,11,39]. The opposite relationship should be true (and it is) for the germ cell tumours. In support of this assumption, the exome-wide sequencing of seminomas, with the exception of driver mutations KRAS and KIT (the latter are specific for primordial germ cells) revealed a low rate of passenger mutations, in comparison with somatic tumours [40]. It suggests that after getting the driver mutation, cancer basically develops as an adaptive reprogramming process. The reprogramming component of the triple-negative breast cancer chemoresistance was recently confirmed in a single-cell transcriptome analysis [41]. In case of colon cancer, where the tumour suppressor APC loss and acquisition of driver mutations KRAS or BRAF occur in adenoma [42], while the exaggerated chromosome and microsatellite instability develop with tumour progression and loss of p53 function [43], the secondary stochastic process partly overlaps and masks the germinative initiation by triploidy. Therefore, the finding of even a small XXY/XX,-Y triploid fraction should be investigated as a possible diagnostic marker for the early stage colorectal cancer in male patients.

However, the question arises, why just triploidy (but not tetraploidy, from which it apparently arises through meiosis) as a whole genome change is associated with cancer origin, its development and resistance to chemotherapy? Moreover, our observations on breast cancer showed that triploidy can convert from a tiny into dominating tumour stemline after failed chemotherapy [3].

The mechanisms of the propagation of cancer stem cells with odd genome numbers and a cause of the adaptive advantage of triploidy remain unclear as well. A possible key to the triploid karyotype XXY appears to be termed "digyny", which is analysed in relation to cancer in the linked paper (Salmina et al., "Reciprocal exchange of diploidy and triploidy in treatment-resistant human tumours: A Digyny concept", submitted).

5. Conclusions

The analysis of karyotypes of 20 male tumour types from Mitelman database revealed doubled maternal genomes fused with a paternal genome in tight association with near-triploidy, which likely lies in the root of carcinogenesis and further cancer development as an essential component of tumour growth.

Author Contributions: NMV carried out the investigation and statistical data analysis (including writing of Python scripts), and participated in the preparation of the original draft; PZ participated in methodology, data validation, and editing the manuscript; RK - advised on selection, nomenclature and clinical characteristics of the analyzed tumour cohorts, participated in the analysis of results; JE - conceptualised the study, carried out the literature analysis, participated in analysis of the results, drafted and edited the final manuscript.

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