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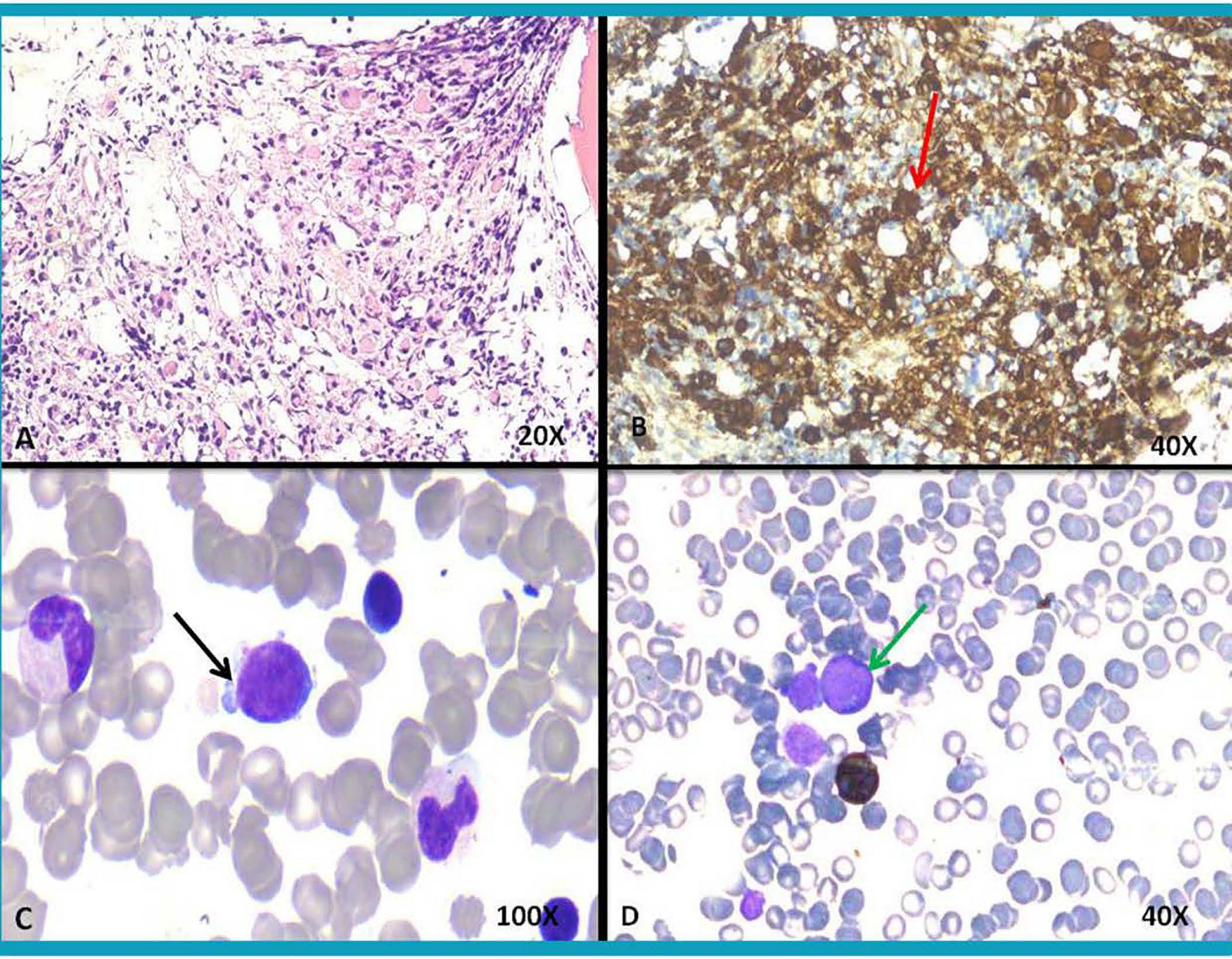

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Current Cancer Reports

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RESEARCH ARTICLE

REVIEW

Curr Cancer Rep, 2021, 3(1): 64-67
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CORRESPONDENCE

Hematogone hyperplasia - A double edged sword

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Hematogones are lymphoid progenitor cells usually comprising $< 1\%$ of marrow nucleated cells. Hematogone hyperplasia is defined as $> 5\%$ hematogones in bone marrow[1].

Hematogone hyperplasia is seen in many reactive and neoplastic conditions such as autoimmune cytopenia(s), post viral infections, Hodgkin/ Non Hodgkin lymphoma, acute myeloid leukaemia, post chemotherapy or stem cell transplant bone marrow[2]. However, occasionally a marked reactive process like hematogone hyperplasia can mask an important underlying morphology. It is further compounded in cases where the diagnostic cells are few in number. Clinching a diagnosis in such cases becomes increasingly difficult.

We here cite a case where hematogone hyperplasia masked an important diagnosis of acute megakaryoblastic leukaemia. This case also highlights the importance of use of multimodalities to diagnose a haematological disorder.

A two-year old girl presented to paediatric out patient department(OPD)with history of bruises over lower leg since 15 days and thrombocytopenia (63×10^9/L). She was being treated for suspected dengue by a non allopathic medicine (*Tinospora Cordifolia*) known to have immunomodulator and antineoplastic effect. The complete blood count was hemoglobin (Hb) 86 g/L, platelet count 16×10^9/L. Immature platelet fraction (IPF)- 4.5%) and total leukocyte count (TLC) 7.8×10^9/L. Abnormal blastoid cells (2%) were reported on peripheral blood smear and bone marrow studies were advised. Bone marrow aspirates received were grossly haemodilute; imprints were also moderately to sparsely cellular. There was presence of atypical cells with fine homogenous chromatin, inconspicuous nucleoli & scant cytoplasm. These constituted 19% of the total nucleated cells. Erythropoiesis was normoblastic with marked paucity of megakaryocytes. In flowcytometric immunophenotypic analysis, hematogone hyperplasia was seen constituting 25% of all acquired cells after excluding doublets and debris (Figure 1). These were recognized by their CD38 and CD19 positivity with sequential maturation pattern visible on CD10 *vs*. CD20 and CD10 *vs*. CD38 plots. Blasts expressing CD7 and CD13/33 were also identified and comprised 2.5% of the total events. Surprisingly, bone marrow biopsy revealed MF grade 2 to 3 fibrosis, megakaryocytic hyperplasia with abnormal megakaryocytes, micromegakaryocytes and megakaryoblasts. Immunohistochemistry of CD61 highlighted megakaryocytes and megakaryoblasts (Figure 2(A) and (B)). Retrospectively bone marrow aspirate slides revealed occasional blasts with cytoplasmic blebbing. A diagnosis of acute megakaryoblastic leukaemia (AML-M7) was considered. A repeat bone marrow study was advised after the effects of the medicine had weaned off.

Repeat bone marrow biopsy was done 20 days later with Hb 125 g/L, platelet count 39×10^9/Land TLC 12 $\times 10^9$/L There were 28% circulating blasts in the peripheral blood. Bone marrow aspirates were poorly cellular with an increase in blasts comprising 30% of the total marrow nucleated cells. Blasts were intermediate to large in size with high nuclear to cytoplasmic ratio, round to oval regular nuclei, fine chromatin, 1-2 prominent nucleoli and appreciable amount of pale basophilic cytoplasm with cytoplasmic blebbing. They were negative for myeloperoxidase stain (Figure 2(C) and (D)). Accompanying hematopoietic cells were myeloid, erythroid precursors and lymphocytes. Flowcytometric analysis of the aspirate revealed 24.0% population in the CD45 dim blast region (Figure 3). These blasts were cytoplasmic MPO negative with CD33, CD117 and cytoplasmic CD41a positivity confirming them to be megakaryoblasts.

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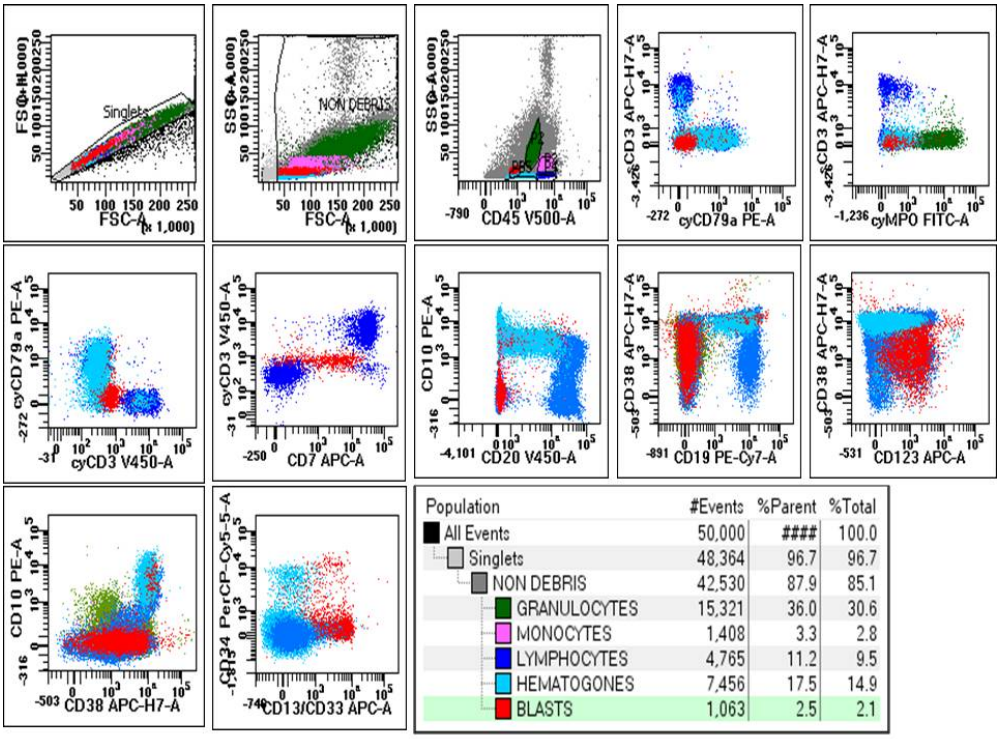

Figure 1. Flowcytometric dot plots at initial presentation with hematogone hyperplasia with 2.5% blasts. Hematogones were CD10, CD20, CD38, CD19 and CD34 positive and show sequential maturation pattern. Blasts were CD7 and CD13/CD33 positive

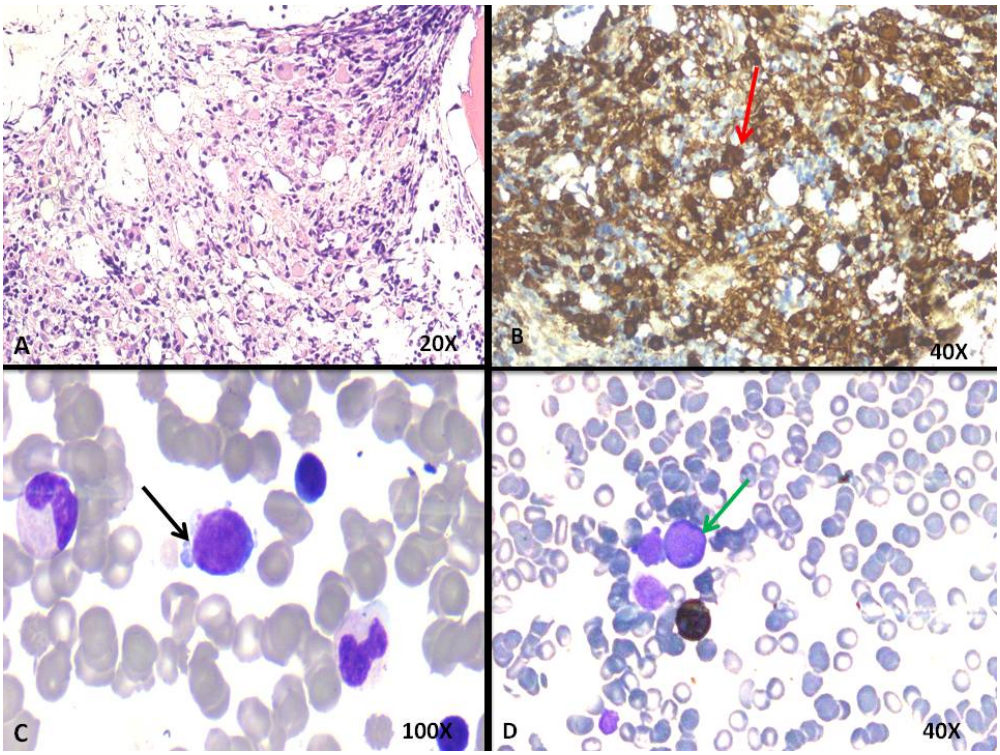

Figure 2. Histomicrographs showing (A) Bone marrow biopsy at the initial presentation with megakaryocytic hyperplasia, abnormal megakaryocytes, micromegakaryocytes and megakaryoblasts along with marrow fibrosis; (B) Immunohistochemistry for CD61 highlighted megakaryoblasts and megakaryocytes; (C) Repeat bone marrow aspirates with megakaryoblasts (intermediate to large in size with high nuclear to cytoplasmic ratio, round to oval regular nuclei, fine chromatin, 1-2 prominent nucleoli and appreciable amount of pale basophilic cytoplasm with cytoplasmic blebbing); (D) Myeloperoxidase negative blasts

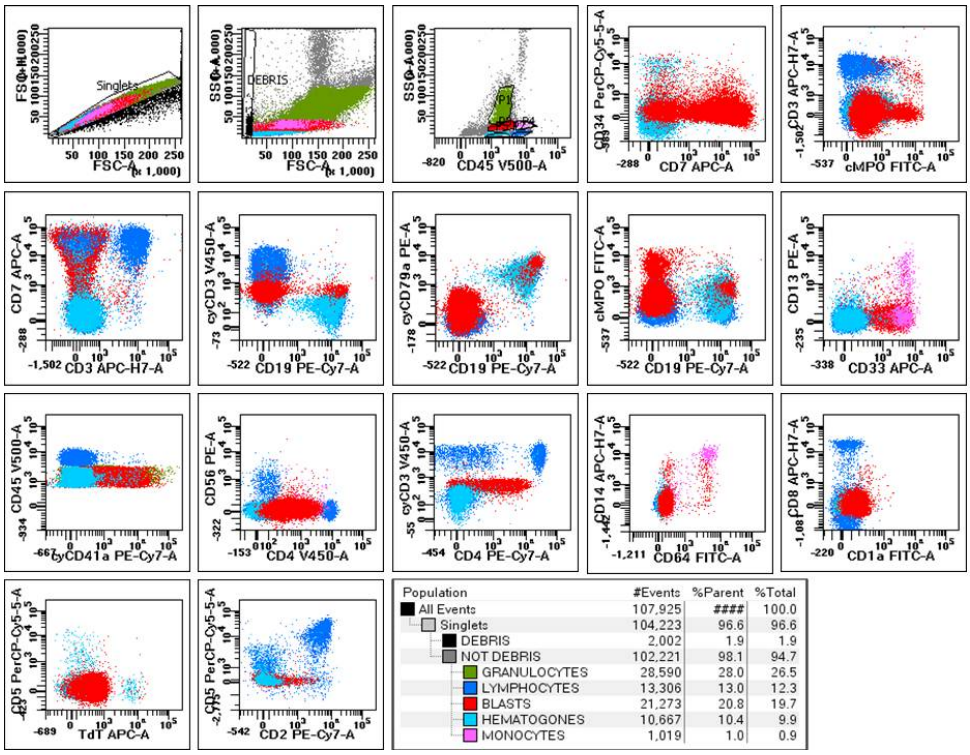

Figure 3. Flowcytometric dot plots of repeat aspirate with 24% blasts. These blasts were CD34, CD117, cytoplasmic CD41, CD71, CD33, HLA-DR, CD123, CD4, CD7 positive

These had aberrant CD7 and CD 4 expression. These were positive for CD34, CD71, HLA-DR and CD123 and negative for B lineage (CD79a and CD19); T lineage (cytoplasmic and surface CD3, CD2, CD8, and CD5) and monocytic (CD11b, CD56, CD14 and CD64) markers. In addition, there were 10.8% hematogones. The final diagnosis of acute megakaryoblastic leukaemia with aberrant CD7 and CD4 expression was rendered. Cytogenetics and molecular studies reported normal karyotype. She was given 4 cycles of chemotherapy according to COG protocol. Bone marrow studies done 3 months later showed morphological remission with 0.1% minimal residual disease. However subsequently the child went in relapse and succumbed to disease.

Hematogones even though is a marrow regenerative response, can camouflage the underlying pathology especially such as in megakaryoblastic leukaemia where due to marrow fibrosis diagnostic blasts are sparsely present in the peripheral blood and bone marrow. In addition, because of intake of unregulated medicines, presence of hematogone hyperplasia creates a further confusion of lymphoblasts creating a diagnostic dilemma.

A comprehensive analysis of literature was done from 1994-2020 and three authors[3–5] have reported similar hindrance in the diagnosis of acute megakaryoblastic leukaemia because of presence of hematogones. Anton-Harisi *et al.*[4] reported 2 cases where there was either preferential uptake of hematogones owing to marrow fibrosis or there was dry tap and flowcytometry was repeatedly inconclusive. Repeated bone marrow aspirations were done to arrive at final diagnosis delaying the treatment. In a case study by Chaudhari *et al.*[5] diagnosis of pre-B ALL was mistakenly made on flowcytometry when patient was not responding to chemotherapy, repeat aspirate and biopsy were done. On immunohistochemistry the blasts were positive for CD61, factor VIII, CD117 and HLADR and final diagnosis of acute megakaryocytic leukaemia was reported.

In the era of multiparametric flowcytometry many centres perform bone marrow biopsy only in cases of dry tap or diagnostic uncertainty[6]. However, this case reemphasises the importance of biopsy which gives a complete picture in context to number, morphology and distribution of cells. Though flowcytometry can pickup and analyse markers on small number of cells but bone marrow biopsy together with immunohistochemistry can supplement and give confidence in making a final diagnosis. Bone marrow regenerative changes are commonly associated with underlying haematological malignancy and these can divert our attention from the main pathology. Identification and employment of templates for all normal hematopoietic elements of bone marrow including mast cells, plasmacytoid dendritic cells, basophils, hematogones and normal myeloid progenitors can help

in identification of abnormal cells with unfamiliar phenotype and differentiate them from the normal elements present in response to marrow regeneration. Employing this strategy will improve diagnostic accuracy and prevent misinterpretation of normal hemopoietic elements which are increased in reactive or regenerative bone marrows.

Take home message from this case is to employ larger panel of antibody markers when the suspicion of malignancy is high and the cellularity of sample is low. Correlation of flowcytometric findings with morphology especially bone marrow biopsy and immunohistochemistry is required. Awareness of such infrequent presentations will help us in scrutinizing cases extensively and prevent fallacies or delay in diagnosis.

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The authors' contributions to this work are as follows: Dr. Aditi Kundoo drafted manuscript; Dr. Sabina Langer and Dr. Jyoti Kotwal worked up and diagnosed the case; Dr. Divij Sachdeva and Dr. Anupam Sachdeva treating physician.

Conflict of interest

There is no conflict of interest.

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HYPOTHESIS

DNA bioelectric field: a futuristic bioelectric marker of cancer, aging and death – A working hypothesis

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Editor's Note

Bio-electrical phenomena were first discovered by Luigi Galvani in the 18th century. With the development of molecular and systems biology research in the last five decades, nowadays the comprehensive understanding of cell behaviors based on a combination of genetics, physics and physiology seems ready to come out at one's call on a bioelectrical conceptualization of cells, especially, recent reports demonstrated that externally applied electrical fields can modulate multicellular processes such as regeneration in plant and vertebrate tissue. All these provide not only plausible explanations for many cell behaviors, but also a new framework to re-formulate much of the existing knowledge in cell physiology, i.e. electrical and chemical potential differences across cellular membranes, or electrochemical gradients (ion motive forces, IMFs) and membrane potential (MP). Interestingly, increasing findings at molecular levels directly lead to the recent proposition that multicellular organization and development more broadly, can, and should, be studied as a bioelectrical paradigm. This framework offers a new synthesis bridging molecular studies with a bioelectrical basis of cellular physiology. The resulting science can have a transformative effect on our understanding of cellular behaviors and pave a novel way to its direct control through predictive bioelectrical marking and/or engineering. Briefly, bioelectricity has become a holistic approach to understand diverse cell behaviors, even sub-cellular events. Telomeres, a specialized DNA-protein structure with a repetitive sequence of DNA at the ends of eukaryotic chromosome, play important role in keeping chromosome intact and genome stability. DNA end replication creates a 3′ single-stranded overhang at each end of the linear chromosome. The 3′ overhang fold back and invade into the dsDNA region of telomere to form loop structure avoiding potential damage on DNA. Usually, telomere length gets shortened after each round of replication, till becomes critically short and unable to form the loop. So the telomere integrity depends on telomere length maintenance and genome stability, the so-called telomere homeostasis. Recently, telomere homeostasis has gained more attention, because its persistent imbalance will result in a spectrum of disorders -telomeropathies, such as dyskeratosis congenita (DKC), aplastic anemia, fanconi anemia and cancer, etc. This background provides an excellent opportunity to put forward novel hypothesis and establish novel predictive, prognostic and therapeutic biomarkers differentially in different cell types or as a combined bioelectric marker for "whole-body" as a derivation of mathematical formulations. The following hypothesis is a good case in point, which suggested DNA's bioelectric field as a novel bioelectric marker for prognostic and diagnostic purposes in researches of cancer, aging, surgery grafts and rejuvenation for the first time. It may open new areas of research on the neglected capacity of telomere and DNA research in diagnosis of a broad array of diseases, physiologic and pathologic conditions. This hypothesis is necessary for designing tailor-made micro-electrochemical impedance spectroscopy technologies, and consequently, pilot studies designed a priori are needed to test the hypothesis. CCR editorial office looks forward to further active exploration of relevant aspects from scientists in basic and clinic research all over the world.

Abstract: Telomeres are associated with the ends of DNA double strands. The lengths of the telomeres are controlled by the telomerase enzyme. The shortening of the telomeres is known to relate to aging. In cancers, telomere lengths are abnormally short. Telomeres could act as buffers shielding the part of DNA coding for the proteins. For cancer cells, germ cells and stem cells, the length of the telomeres is not varying. There is an analogy with microtubules, which are highly dynamical and carry a longitudinal electric field, whose strength correlates with the microtubule length. Could sticky ends generate a longitudinal field along DNA double strand with strength determined by the lengths of the sticky ends? In the standard picture, the flux of the longitudinal electric field would be proportional to the difference of the negative charges associated with the sticky ends. In Topological Geometrodynamics (TGD) framework, DNA strands are accompanied by the dark analog of DNA with codons realized as 3-proton units at magnetic flux tubes parallel to DNA strands and neutralizing the negative charge of ordinary DNA except at the sticky ends. This allows considering the possibility that opposite sticky ends carry opposite charges generating a longitudinal electric field along the magnetic flux tube associated with the system. DNA/Telomere bioelectric field could serve as a novel bioelectric marker to be used for prognostic and diagnostic purposes in researches of cancer, aging, surgery grafts and rejuvenation. We propsed that DNA bioelectric field can be used as a futuristic bioelectric marker of cancer, aging and death.

Keywords: bioelectric marker, cancer, aging, rejuvenation, telomere, early diagnosis

1 Introduction

The motivation for this article was the question whether there could be a longitudinal electric field associated with DNA and whether the reduction of its strength could serve as a bioelectric marker of cancer, aging and death. This could be the case if the length of DNA correlates with the strength of this electric field. The natural question is whether the length of the negatively charged sticky end of DNA could determine the strength of this electric field.

1.1 Could DNA be a ferroelectret and could the length of sticky ends control the strength of the longitudinal electric field?

DNAs and RNAs have bioelectrets [1,2] but the question whether they are bioferroelectrets possessing a constant longitudinal electric field in the absence of external electric field is an open question.

Telomeres are associated with the ends of DNA double strands. The lengths of telomeres are controlled by the telomerase enzyme. The shortening of telomeres is known to relate to aging. For cancer cells, germ cells and stem cells the length of the telomeres is not varying. In cancer their lengths are abnormally short. Telomeres could act as buffers shielding the part of DNA coding for proteins. Telomeres have “sticky ends” assignable only to the second DNA strand and carrying negative charge. What their function could be? Could telomere lengths correlate with the lengths of the sticky ends and what could control their lengths?

There is an analogy with microtubules, which are highly dynamical and carry a longitudinal electric field, whose strength correlates with the microtubule length. Could the sticky ends generate a longitudinal field along DNA double strand with strength determined by the lengths of the sticky ends? In the standard picture the flux of the longitudinal electric field would be proportional to the difference of the negative charges associated with the sticky ends.

In a conceptual framework based on Topological Geometrodynamics (TGD) [3,4], which is a proposal for a unification of fundamental interactions inspiring a vision about consciousness and quantum biology, DNA strands are accompanied by the dark analog of DNA with codons realized as 3-proton units neutralizing the negative charge of ordinary DNA except at sticky ends. If the dark double strand accompanies also the sticky end, the total charge is positive. If not, it is negative. This allows to consider the possibility that opposite sticky ends have opposite charges so that there is a long dipole like entity carrying longitudinal electric flux proportional to the common length of sticky ends.

1.1.1 Experimental signatures

Also in standard physics based picture (no dark DNA), an external electric field created by the polarization of the nucleotides A, T, C, G in an external electric field is possible [2] . This would mean electrect property, not yet ferroelectricity. The model for the phenomenon suggests that ferro-electricity could result in the sense that the polarization is non-vanishing also

in absence of the external electric field so that the nucleotide rather than entire DNA strand - would be an electric analog of ferromagnet.

In this case the behavior in the external electric field is different from that for fer- roelectric DNA double strand: DNA double strand itself would not experience a direct torque in the external electric field. The effective polarization *per* nucleotide predicted by TGD is at least by a factor 2.5-7.5 stronger than standard model polarizations so that the model can be tested. Furthermore, ferroelectricity of DNA in TGD sense requires DNA double strands and would be present for single DNA strand.

The secod testable prediction is the possibility of currents running along DNA double strand in the longitudinal electric field even without external electric field. External field would however add to the ferroelectric field of oriented DNA double strands and lead to an anomalously high conductivity. Another test would be based on the ferroelectret property of living tissues, which could be caused both by DNA and protein ferro-electricity. Living tissues are indeed known that be ferroelectres as the phenomena of pyroelectricity, piezoelectrity -studied first by [1] and the polarization in an external electric field demonstrate. Ahlenstaedt proposed that the permanent dipole like character (ferroelectricity) of the linear biomolecules gives rise to their bioferroelectricity.

1.1.2 Connection with consciousness

An analogy with the findings of Becker [5] about the electric fields along the body axis emerges. Becker found that the direction of this field determines whether the organism is awake or in a sleep state. The weakening of these fields leads to aloss of consciousness. TGD inspired theory of consciousness predicts that even sysems like DNA can be conscious and the fractality of TGD Universe suggests that the physical correlates of consciousness are same in all scales.

Could the direction and strength of the electric field of DNA correlate with consciousness at this level? In TGD based quantum measurement theory extending to a theory of consciousness the arrow of time changes in “big” state function reductions (BSFRs), which mean “death” and “reincarnation” with opposite arrow of time [3]. By the tensorial properies of electromagnetic field tensor the arrow of time correlates also with the direction of the electric field. This leads to ask whether the change of the arrow of time in BSFR could change the direction of the DNA bioelectric field, and one ends up with a simple mechanism for this based on the analog of Becker’s DC currents along DNA as proton currents.

1.2 Telomere length, cancer, and DNA ferroelectricity

Compelling evidence suggest that there is an inverse relationship between telomere length and both different types of cancer incidence and mortality [6–8] suggesting that the control of telomere length by telomerase enzyme is impaired [9, 10].

Almost in all cancer cells, telomere length is shortened [11, 12]. Telomere shortening accompanies ageing [13]. Even in stem cells, except for embryonic stem cells and cancer stem cells, there are overwhelming evidence that telomere shortening occurs during replicative ageing, though at a lower rate than that in normal somatic cells [14] .

In this picture, the simplest possibility is that telomeres act as buffers, and the strength of the longitudinal electric field controlled by the length of sticky ends controls the length of telomeres and thus of DNA. Sticky ends would be the key control knobs used by telomerase enzyme, and magnetic body (MB) of the system would be the ultimate controller.

Apart from some exceptions, telomere length in DNA is shortened in almost all cell types during aging and some diseases, based on the level of telomerase activity or its absence [8]. Ageing could be purposefully induced since eternal life would be a metabolic catastrophe from the perspective of population overgrowth and evolution [15].

This motivated us to propose the hypothesis that DNA bioelectricity changes over time and depends on disease progression and severity. This provides an excellent opportunity to establish novel predictive, prognostic and therapeutic biomarkers differentially in different cell types or as a combined bioelectric marker for “whole-body” as a derivation of mathematical formulations. This hypothesis is necessary for designing tailor-made microelectrochemical impedance spectroscopy technologies, and consequently, pilot studies designed *a priori* are needed to test our hypothesis. Along with replication of well-designed pilot study with a more diverse population and larger sample size, it will be needed to address questions about cut-offs or personalized normal ranges for differential and mean whole-body DNA’s bioelectric field in a longitudinal study in a prospective manner. With this brief background, the aim of this paper is to suggest DNA bioelectric field as a novel bioelectric marker to be used for prognostic and

diagnostic purposes in researches of cancer, aging, surgery grafts and rejuvenation, for the first time.

2 Could the sticky ends make DNA double strand a ferro-electret?

In the sequel the idea that sticky ends make the DNA double strand + its dark counterpart a ferro-electret carrying longitudinal electric field is considered. The longitudinal electric field is non-vanishing also in standard framework without dark DNA if the lengths at the ends of the DNA double strand are different. This field would be analogous to the electric field along the body axis. As Becker found [5], its direction determines whether the system is in wake-up state or sleep and the same could be true also for DNA+ dark DNA system.

2.1 Different ends of DNA double strand

There are Wikipedia articles about telomeres [16] and about the so called overhangs/sticky ends at their ends [17]. The video about telomeres and sticky ends [18] is very helpful for a non-specialist.

For readers' convenience is appropriate to summarize first the basic facts about telomeres and sticky ends. There is a variety of different ends of DNA double strand and of telomere.

(1) Blunt ends contain two paired bases so that they do not define a full codon.

$5'$ - CTGATCTGACTGATGCGTATGCTAGT - $3'$
$3'$ - GACTAGACTGACTACGCATACGATCA - $5'$

Straight cut by exonuclease enzyme produce blunt ends.

(2) Overhangs are short, minimally just one nucleotide A in 3' end: one could have for instance following configuration

$5'$ - ATCTGACTA - $3'$
$3'$ - TAGACTGA - $5'$

Overhangs are most often palindromic.

(3) An example of longer sticky end is following:

$5'$ - ATCTGACT 3^{J} - TAGACTGACTACG

The length of the unpaired portion of sticky end can be hundreds of nucleotides.

(4) Frayed ends correspond to sequence of basic pairs breaking the A-T, C-G pairing rules.

$5'$ - ATCTGACTAGGCA - $3'$
$3'$ - TAGACTGACTACG - $5'$

2.2 Empirical evidence for the ferroelectret property of DNA

To the best of our knowledge, there is no reported evidence for longitudinal static electric fields in DNA in an extensive Web search. This might be simply because of inability to measure them in the past. Indeed, a model for DNA nucleotides A,T,C,G as ferroelectrets based solely on [19] and would imply that also DNA can be ferroelectret. This could in a special case give rise to a longitudinal electric field, and if there is an electric field in the absence of external electric field (spontaneous ferroelectricity), it could be also in the direction of DNA strand.

The reported existence of electric currents along DNA perhaps analogous to Becker's DC currents is one indirect evidence for the longitudinal electric field. A very interesting test would be so called DNA crystals [20]. See also the popular article [21] in electric field, heated, or put under mechanical stress.

DNA is analogous like cell interior being negatively charged with one negative charge per nucleotide assignable to the phosphate. The stability of DNA against Coulomb force is however not well-understood and TGD would solve the problem with a pairing of DNA strand with a parallel helical flux tube carrying 3 dark protons per codon with dark proton triplet realizing genetic codon. Ordinary chemical codons would be a secondary representation of the code. Could this make possible ferroelectret property of DNA?

2.3 Could the sticky ends of the telomeres give rise to a longitudinal electric field along DNA?

In the standard picture about DNA, different negative charges at the sticky ends could give a longitudinal electric field proportional to the difference of the charges. DNA double strand would however have a net charge now. Second possibility is that the nucleotides behave as

dipoles even in the absence of the external electric field. If these dipoles are forced to be parallel to DNA by an external electric field they give rise to a longitudinal electric field.

TGD based view is that DNA is paired with dark analog of DNA. This view leads to the suggestion that sticky ends/overhangs give rise to positive or negative charges at the end of DNA and that opposites at the ends of DNA generate strong longitudinal electric field along DNA. For DNA with blunt ends there would be no electric field.

What would be needed for chromosome as dipole like entity is that the ends of the chromosome carrying the telomeres have charges of opposite sign: in the simplest case they would have the same magnitude so that one would have a dipole.

2.3.1 Could telomeres be analogous to microtubules?

Microtubules are highly dynamical having a varying length. They also have a longitudinal electric field [22, 23]. Likewise, the the ends of chromosomes are dynamical and their length is changing and controlled by the telomerase enzyme [11, 24]. Could telomeres or entire chromosomes be analogous to microtubules? Could chromosomes [25] carry longitudinal electric fields? That would not be surprising since living matter is populated by ferroelectrets [26].

Remark: The option that only telomeres could carry these fields would require that the joint between the coding portion of DNA and telomere is charged. This does not look natural.

Due to the properties of the electric field under time reversal, the direction of the bioelectric field would in TGD Universe correlate with the arrow of time [3,26] changing in "big" (ordinary) state function reductions (BSFRs) meaning "death" or "falling asleep" and reincarnation with an opposite arrow of time. In particular, sleep could correspond to conscious experience but with a different arrow of time at some level of the hierarchy of layers of MB [27] serving as master controlling the biological body (BB).

Remark: The hierarchy of Planck constants $h_{eff} = nh_0$ labelling phases of ordinary matter behaving like dark matter predicts [28, 29] macroscopic quantum coherence explaining the coherence of biomatter. This allow BSFRs in arbitrarily long length and time scales, for instance, the scales of chromosomes.

The first guess motivated by the findings of Becker about bioelectric fields [5] is that when the telomere shortens, the electric field associated with DNA weakens, and eventually the organism dies [13] . Telomere length is controlled by telomerase enzyme and for stem cells, germ cells and cancer cells the shortening does not occur.

Telomeres are dynamical and could somehow provide DNA with a longitudinal electric field closely related to this dynamics. The strength of the electric field associated with the DNA double strand could correlate with the properties of telomeres and in particlar, with the lengths of their negatively charged sticky ends at the ends of the chromosome.

2.3.2 The TGD based model for DNA as ferroelectret

Although most of the telomere has a normal base-pairing, there is an additional unpaired nucleotide sequence - overhang - associated with either strand. In the minimal case, it is just one nucleotide A. What could this mean in TGD framework: could it give the desired constant electric field along DNA strand? Is its strength proportional to the length of the overhang determined by the number of its nucleotides? There would be 1 negative charge *per* nucleotide.

(1) Suppose that both strands are accompanied by dark DNA strands parallel to them and having opposite charge neutralizing the DNA in the scale of this pairing. Dark codon would be identified as a 3-proton unit. Dark RNA, tRNA and amino-acids are predicted. Vertebrate genetic code is predicted correctly in the sense that the number of DNA codons corresponding to given dark amino-acid is the same as for vertebrate genetic code [29, 30].

(2) What could be the counterpart of the sticky end for dark DNA sequence? Suppose that the dark DNA strands be equally long so that there would be no symmetry breaking. This leaves two natural options for a given sticky end.

(a) Both dark DNA strands have portions associated with the sticky end. Since the sticky end/overhang would be neutralized, this would give for the end of the double strand a positive charge $Q = ne$, n is the number of nucleotides in the sticky end.

(b) Both dark DNA strand portions are missing at the sticky end. Now the charge would be negative and equal to the charge $Q = -ne$ of the sticky end.

(3) The magnitude of the electric field along DNA flux tube created by a single sticky end would be

$$E = \frac{Q}{S} = \frac{ne}{S}$$

where S is the thickness of the system DNA + dark DNA. The fields of the sticky ends sum up and there would be a net electric field along DNA double strand +dark DNA given by

$$E = \frac{Q_1 - Q_2}{S} = \frac{e\,(n_1 - n)}{S}$$

One can consider two options:

Option I: There is dark DNA present (TGD option) and the situation is a) at the first end of the chromosome and b) at the opposite end. One obtains opposite signs of charges *Q1 = n1e* and *Q2 = -n2e* and electric field is *E = (n1 + n2)e/S*.

Option II: There is no dark DNA (standard physics option). The charges at the sticky ends are negative and one has *E = e(n1 - n2)/S*.

(4) The video about telomeres [18] suggests that the sticky ends are associated with different DNA strands and are of the same length. For the standard physics option (no dark DNA) charges at the sticky ends have the same sign and one has *E = e(n1 -n2)/S*. The field vanishes for **Option II** and equals to *E = 2n/S* for **Option I.** This field would be quite strong. The electric fields at opposite ends of the chromosome sum up and cancel each other along DNA if the charges are of the same sign : there is however positive interaction energy causing a repulsive force. For the TGD option the Coulomb energy is negative. For the standard physics option it would be positive and would not favor the stability of DNA.

2.3.3 Quantitative estimates

In the sequel some simple quantitative estimates are performed.

(1) *Minimization of electrostatic energy taking into account only the nearest neighbor interactions*

The system must minimize its electrostatic energy to be stable. Assume that the charges of the overhangs are opposite: $n_1 \neq$ -n_2 = n. For the more general situation with $n_1 = n_2$. For the same sign for n_1 and n_2 there would be repulsion between the ends of DNA.

(a) In this case overhangs would give a negative contribution to the electrostatic energy of the system.

$$E_{ends} = -\frac{\mathrm{n^2 e^2\,L}}{\mathrm{S}}$$

where L is the length of DNA double strand without overhangs and S is it transversal area. Otherwise the contribution is positive.

(b) The negative electrostatic energies between dark strand and ordinary strand with opposite charges. There are two pairs of this kind. In the first approximation one has:

$$E_{\mathrm{OD}} = -2N\frac{e^2}{\mathrm{R_{OD}}}$$

N is the total number of nucleotides in DNA without overhangs and R_{OD} is the distance between dark and ordinary DNA strands. One has *N = (dn/dl)L*, where *dn/dl* is the number of codons per unit length. One has approximately *dn/dl* = 10 nucleotides *per* nanometer.

This gives:

$$E_{OD} = -2\frac{(dn/dl)e^2L}{R_{OD}}$$

The ratio of the two negative contributions tending to stabilize the system is:

$$r = \frac{E_{OD}}{E_{ends}} = 2\frac{\left(\frac{dn}{dl}\right)S}{R_{OD}} \cong \frac{20S}{nm} \times \mathrm{R_{OD}}$$

(c) There are positive electrostatic interaction energies between dark strands with distance *R = R_{DD}* and ordinary strands with distance *R = R_{OO}*. The energy is given by:

$$E = \frac{Ne^2}{R} = \frac{\left(\frac{dn}{dl}\right)e^2L}{R}$$

The total contribution to the electrostatic energy is positive and given by:

$$E_{OO} + E_{DD} = (dn/dl)e^2L \times \left(\frac{1}{R_{OO}} + \frac{1}{R_{DD}}\right)$$

The total electrostatic energy in this approximation is:

$$E = e^2L - \frac{n^2}{S} - 2\left(\frac{dn}{dl}\right)\left(\frac{1}{R_{OD}} - \frac{1}{R_{OO}} - \frac{1}{R_{DD}}\right)$$

(d) The generalized electrostatic force in the longitudinal direction is given by:

$$F = -\frac{dE}{dL} = -e^2\left[\frac{n^2}{S} - 2\left(\frac{dn}{dl}\right)\left(\frac{1}{R_{OD}} - \frac{1}{R_{OO}} - \frac{1}{R_{DD}}\right)\right]$$

For $n > n_{min}$ DNA tends to get longer and for $n < n_{min}$ it tends to get shorter.

(e) In equilibrium this force must vanish. $F = 0$ condition fixes the number n of nucleotides in the sticky end:

$$n^2 = n_0^2 = \left(\frac{dn}{dl}\right) \times S\left[\frac{2}{R_{OD}} + \frac{1}{R_{OO}} + \frac{1}{R_{DD}}\right]$$

This gives:

$$n = n_{\rm min} = \sqrt{\left(\frac{dn}{dl}\right) S/R_{DD}} \times \sqrt{-2\frac{R_{DD}}{R_{OD}} + \frac{R_{DD}}{R_{OO}} + 1} = \sqrt{\frac{10S}{R_{DD}nm}}\sqrt{-2\frac{R_{DD}}{R_{OD}} + \frac{R_{DD}}{R_{OO}} + 1}$$

Note that the condition $n_{min} > 0$ requires that without the overhangs at the end, the configuration would be unstable. So

$$2\frac{R_{DD}}{R_{OD}} \geq \frac{R_{DD}}{R_{OO}} + 1$$

must hold true. Since the right-hand side is larger than unity one must have $2R_{DD} > R_{OO}$. As special case one could have a maximally symmetric DODO type configuration with $R_{OO} = R_{DD} = R_{OD}$ for which the above inequality becomes equality and one has $n = 0$. $n = 1$ is realized rather generally and is maximally near to this situation.

(f) n would not depend on the length L of the chromosome in the approximation taking into account only the nearest neighbor interactions between various DNA codons. Taking them into account implies that the electrostatic energy is a nonlinear function of L and n_{min} is predicted to depend on L - probably the dependence is weak suggesting that the dependence of $L = L(coding) + L(telomere)$ - or actually the telomere length $L(telomere)$ - on n_{min} is strong so that it would be an ideal control variable.

(g) The increase of the length n of the overhang creates a force increasing the length of DNA and its reduction does the opposite. One can say the situation is critical and that $n = n_{min}$ stabilizes the situation. The reduction of the length of overhang below critical value would have disastrous effect.

This model is certainly not the only one that one can imagine and involves drastic approximations since only the nearest neighbour Coulomb interactions has been taken into account. Also the sticky ends of the chromosome could have different lengths and thus charges so that the chromosome would have a net charge and the stable length for DNA would depend on this charge.

Also the distances between various DNA strands serve as parameters and the stable length depends on these parameters: these parameters could depend on chemical param- eters like pH and thermo-dynamical parameters. The length of the sticky end is expected to vary also during the life span of the chromosome and also depend on how many DNA replications preceded the generation of the chromosome. The length of the sticky end has spectrum and implies a spectrum for the telomere length since the length $L(coding)$ of the coding part of the chromosome cannot be changed. In the linear approximation all lengths $L = L(coding) + L(telomere)$ are allowed and if the corrections are small, $L(telomere)$ is very sensitive to $L(stickyend)$.

The length of the sticky end rather than the length of the telomere would be the primary controller. The quite high strength of the longitudinal electric field is a surprise. An interesting prediction is that prokaryotes with circular DNA strands would have no wake-up-sleep cycle like eukaryotes. Viruses however have both circular and open strands.

(2) *Minimization of the electrostatic energy taking into account interaction between non-nearest neighbors*

What kind of corrections the inclusion of the Coulomb interactions of charges which are not nearest neighbors could bring in?

(a) Nearest neighbors have been identified as neighbors in transversal direction and it has been assumed that only DNA-DNA and DDNA-DDNA, and DNA-DDNA interactions matter. A better approximation would take into account the repulsive nearest-neighbor interactions between phosphates and between dark protons along dark DNA. Same applies to DNA-DDNA interactions.

(b) All these terms give a contribution proportional to L and mean only a scaling of the parameter n_0, whose order of magnitude remains the same and by the presence of the longitudinal dipole electric field can be positive.

(c) Consider the contribution of the interactions of given DNA codon and DDNA codon with the non-nearest neighbors along DNA and dark DNA. These interactions can be regarded as dipole and higher multiple interactions since the total charges of the codon pair DNA + DDNA vanish. In the lowest order approximation dipole-dipole interactions depending on the distance r between dipoles like $1/r^3$.

(d) Simple dimensional arguments give the general form of the dipole contributions. By dimensional considerations alone, the sum over dipole interaction energies for a given codon or nucleotide gives a contribution proportional to $1/L^2$. Summing over these contributions gives a total contribution proportional to $1/L$.

The dipole contribution is proportional to $(dn/dl)^2$, to the square of the dipole moments of a given nucleotide (codon). Since dipole moments are of the order eR, R the transversal scale of DNA+DDNA system, individual dipole-dipole interaction energy is proportional to e^2S.

Therefore the Coulomb interaction energy would be of the general form

$$E = \frac{e^2 L}{S}\left[-n^2 + n_0^2\right] + ke^2\left(\frac{dn}{dl}\right)^2\frac{S}{L}$$

where k is a numerical factor determined by the details of the model. Note that dark protons forming a dark variant of ordinary nucleus are expected to have also counterparts of strong interactions expected to be short ranged.

(e) The minimization of energy would give:

$$F = -\frac{dE}{dL} = \frac{e^2}{S}\left[-n^2 + n_0^2\right] - ke^2(dn/dl)^2\frac{S}{L^2}\Big)\Big] = 0$$

This gives for $L(n)$:

$$L(n) = \frac{dn}{dl}S\sqrt{\frac{k}{-n^2 + n_0^2}}$$

The condition that the argument of square root in non-negative, implies that one must have either ($k > 0$, $n < n_0$) or ($k < 0$, $n > n_0$). $n < n_0$ option seems to be the physical one.

(f) $n < n_0$ requires $k > 0$ so that the dipole interaction energy is positive. For n $\to$ 0 , L approaches to:

$$L(0) = \frac{dn}{dl}S\sqrt{\frac{k}{n_0^2}}$$

$L(0)$ could correspond to the length for the coding part of DNA (no telomere is allowed). At the limit $n \to \infty L(0)$ approaches infinite value and the length of the telomere becomes extremely sensitive to the value of n and n becomes an ideal control variable.

For $n > n_0$ one must have $k < 0$ meaning that the contribution of the dipole-dipole interactions to the total energy is negative. The stable DNA length shortens roughly like $L \propto 1/n$ as n increases: this does not conform with the intuitive picture.

2.4 Tests for the TGD based model of DNA as ferroelectret

The standard physics view is that the possible ferroelectricity for DNA is due to the instantaneous polarization of codons A,T,C,G in external field which is proportional to electric field E if the polarization vanishes for $E = 0$. Ferroelectriy is analogous to spontaneous magnetism that there is electric field also for $E = 0$: this requires permanent electric dipole moments generated by small external field an left when the field is taken to zero.

In [31] a model for the polarizability of nucleotides A,T,C, G is developed based on standard physics so that the external electric field would generate dipole moment for given nucleotide. What one hopes to have is ferro-electric behavior. The model calculations give ferroelectric behavior and a square shaped hysteresis curve. In case of entire DNA each nucleotide would behave independently in inhomogenous electric field with varying direction.

Also in [19] the dipole moments are estimated for both bases and nu- cleotides, and the esimated dipole moments are in the range of 2-6 Debyes ($D = 0.02$ enm) that is 0.04- 0.12 enm. TGD estimate for the electric field is about ne/S, $S = \pi R^2$ the effective area of the flux tube assignable to DNA + dark DNA.

The first thing to notice is that the flux would be along entire DNA, not only the telomere and the overhangs portions carry the charges creating the electric field along DNA. Electric flux flows along DNA. Telomere would be a kind of buffer against the evil world. Overhang/sticky ends could play a key role in control of the arrow of time for DNA. Similar mechanism would be at work at the level of entire body changing the direction of endogenous electric field and leading to wake-up to sleep or *vice versa* [5] .

Suppose that the charges at the opposite ends of DNA are of opposite sign. An unnecessary strong assumption is that they are of the same magnitude. The dipole moment would be roughly given by the difference Q_1 - Q_2 of the charges multiplied by the distance L between ends of the chromosome along the DNA strand. Note that the channeling of electric flux along DNA would be rely on TGD view about space allowing monopole flux tubes whose deformations carry also electric field.

The static electric field would be realized as a conserved electric flux along the entire DNA, not only telomere. The order of magnitude is 10 GV/m for R = 1 nm so that it would be rather strong. The strength of electric field is proportional to $1/R^2$ and R is expected to vary in the range 1-10 nm. Note that $L(151)$ = 10 nm corresponds to the p-adic length scaled the thickness of the DNA coil and chromosome thickness.

The effective dipole moment per nucleotide would be $p \cong ned \cong n \times 0.3$ enm and quantized as multiples of n. The estimate is at most by a factor 2.2-7.5 larger than the estimates from the atomic contributions and would allow selecting between the standard model and TGD based model.

2.4.1 Nanoscopic implications

What could be possible experimental consequences of the proposed electric field? Consider first the situation at the level of single DNA double strand.

(1) The accelerated motion of a test charge along DNA could serve as a test for this option. One can consider both quantum motion without dissipation - perhaps along the dark DNA - and Ohmic current along the ordinary DNA. They would run also in absence of external electric field unlike ordinary Ohmic currents.

These currents could be nanoscopic analogs of the DC currents observed by Becker in body scale and brain scale. If they are steady currents the current is conserved and must return so that a closed current loop is formed. The currents could be also pulselike taking surplus dark protons between ends of the chromosomes and changing the their roles. This would be quantum event associated with BSFR and could mean time reversal.

Electronic (not protonic) currents along DNA [32] have been observed for single DNA strands in an external electric and it is found that the con- ductivity is surprisingly high. In the recent case conduction double strand property and sticky ends would be essential.

(2) How could the current return in steady situation? This question must be answered also for Becker's current. Does the current flow as Ohmic current along ordinary DNA and return back along the dark DNA as non-dissipative current? The proton current along DNA along electric field to negatively charged and dark protons would be accelerating: the quantum description would correspond to a particle in linear potential, which is standard quantum mechanical problem. The larger the charge (the length of the sticky end), the stronger the current. Its magnitude would be quantized being proportional to the length and charge ne of the sticky end. The variation of sticky end length would vary the strength of the current.

The larger the charge (the length of the sticky end), the stronger the current. Its magnitude would be quantized being proportional to the length and charge ne of the sticky end. The variation of sticky end length would vary the strength of the current. There is evidence for proton AC current conduction in the DNA double strandimidazole composite material under anhydrous conditions (no water) in the freqency range 4 Hz - 1 MHz [33]. If the mechanism is the proposed one - probably not - the oscillatory current could correspond to occurrence of BSFRs changing the arrow of time *per* each period of $T = 1/f$. This would predict the current to be $I = 2nef$, where $\pm ne$ are the charges at the ends of the double DNA strand.

2.4.2 How to test whether DNA double strand is ferroelectret?

(1) The measurement of the possible longitudinal electric field of DNA and its correlation with the length of the telomere or of the sticky end would be an interesting expermental project. DNA exconuclease restriction enzyme allowing to cut pieces from the end of either DNA strand could allow creation of desired length of unpaired portion of DNA. Also blunt ends could be created and the prediction is that there is no electric field in this case.

(2) The telomere or the entire DNA would be like a dipole and would interact with external electric fields. One should be able to prepare a DNA sample as an electret so that DNAs would have the same dipole direction and this structure could be put in an electric field allowing measuring the dipole moment of DNA as a macroscopic motion in the field.

The external electric field would give rise to a torque acting on the entire DNA double strand. If nucleotides behave as independent dipoles as the standard physics based model suggests,

this would not be the case and the dipole moments of the nucleotides would only turn in the direction of the external field.

(3) One could also study whether and how the possible DNA dipole moment is affected by the telomerase affecting the length of telomere. The first guess would be that is the length of the sticky end which is affected and that the length of the telomere correlates with this by stability conditions. Pyroelectricity and piezoelectricity and the use of external electric field produce ferroelectrets from various biological tissues [25, 26]. These methods applied to DNA crystals [20] could allow to test the hypothesis.

The measurement of the possible longitudinal electric field of chromosome or DNA double strand and its correlation with its length could serve as an early bioelectric marker: this could be an experimental project. Currently, the measurement of telomere length by quantitative PCR is quite common and for a summary of critical factors and recommendations for assay design, interested readers may see [34]. Also, a full description and protocol for examination of the telomere G-overhang structure in different plant, human and vertebrate models are available [18, 35–37]. However, to the best of our knowledge, this is the first hypothetical paper to suggest DNA/telomere's bioelectric field as an independent marker which may revolutionize a wide array of medical investigations.

2.4.3 Could pyroelectricity, piezoelectricity, or the behavior in external electric fields be used to demonstrate that DNA has a longitudinal internal electric field

One can consider also the consequences at condensed matter level. Athensteadt has found [38] that it is possible to make various tissues of vertebrates piezoelectric or pyroelectric.

Pyroelectric materials [38] are crystals in which the change of the temperature involving thermal energy flow induces a macroscopic electric polarization and therefore electric field making the material ferroelectric. In piezo-electric materials [38] mechanical stress induces a generation of polarization and macroscopic electric field. Also an external electric field can induce polarization producing a ferroelectret.

One can visualize the situation using a triangle having kinetic, electric, and thermal energies as corners. For piezoelectric materials the motion occurs along the edge connect- ing electric and mechanical energy. For pyroelectric materials the motion occurs along the edge connecting electric and thermal energy.

The proposal is that DNA double strand + dark DNA strand carries internal electric field is 1-D ferroelectric aperiodic crystal due to its inherent polarization. One cannot exclude the possibility that also single DNA strand + dark strand has this property. DNA should be *in vivo* state. DNA crystals [20] might allow to test the phenomenon. For instance, it is known that DNA suspended in liquid which is evaporated forms crystal [21]. Could DNA crystals become ferroelectrets by heating or cooling or by applying a mechanical stress or an external electric field?

If this would occur, the interpretation would be that DNA strands become parallel and have parallel electric fields giving rise to ferroelectricity. In the positive case, one could test the hypothesis by using DNA preparations with different values of n for the number of overhang nucleotides: electric field in the ideal situation would be proportional to n if the area density of the parallel DNA strands is the same.

2.5 Medical application of the measurement of bioelectric fields of DNA

Thought experiments can be designed in order to possibly carry out in a sample of volunteer identical twins with quite matched or similar lifestyle to find out any correlation between age and gender- adjusted death rates and cancer measures with differential and mean whole-body DNA bioelectric field, with minimally invasive techniques and data collection to derive a regression equation as a rough estimate. Severity and progression of cancer, time of death and DNA bioelectric field for each sibling can be recorded for analysis and data mining purposes and assessment of prognostic and predictive values.

We suggest that future clinical trials investigating telomere rejuvenation in aging and cancer studies, measure appropriate variables such as DNA bioelectric field, percent of apoptotic and cancer cells, severity and progression of cancer and such as those to yield preliminary data for future interventional trials and ethics committees. Interventional studies in animal models of cancer and aging using telomere rejuvenation techniques would be the first steps to find out any

causal effect of restored DNA's bioelectric field -to level at birth- on therapeutic measures of cancers and aging.

It will be also useful to design a registry for DNA bioelectric field strengths in different cell types at birth (as baseline value), incidence of major cancers by type, and death, to find out prospectively a golden ratio at which highest incidence of cancers and death is recorded, after controlling for compounding factors. Such data in future can be used for telomere rejuvenation in a prophylactic manner, if needed. DNA bioelectric field measure could have some advances of the measurement of telomere length. Being less invasive and preserving the patients ability to undergo possible repeat operations, reasonable cost-effectiveness which allows multiple measurements and replications, lesser inter and intra-subject and observer variations compared to that of other discrete measures due to the continuous nature of electric field measures which additionally allows more reliable and valid comparisons of percentile-effects for DNA bioelectric field restorations or variations on measures of interest, just to mention a few among others.

To set up individualized cut-off values, differential and mean whole-body DNA bioferroelectric field at birth; and for normal range values, data obtained from different age and gender groups can be used as a preliminary start point, respectively.

3 Conclusions

Telomeres bioelectric field could serve as a novel bioelectric marker to be used for prognostic and diagnostic purposes in researches of cancer, aging, surgery grafts and rejuvenation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Matti Pitkänen wrote the initial draft, revised and finalized the paper. Reza Rastmanesh criticized the paper, revised and approved the paper.

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RESEARCH ARTICLE

Predictors of prostate cancer screening among African American men treated at an Academic Medical Center in the Southern United States

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Abstract: **Background**: The controversy surrounding prostate cancer screening, coupled with the high rates of incidence and mortality among African American men, increase the importance of African American men engaging in an informed decision-making process around prostate cancer screening. **Purpose**: To examine predictors of prostate cancer screening via the prostate-specific antigen (PSA) test. Secondary objectives were to examine whether African American men have been screened for prostate cancer; their confidence in making an informed choice about whether PSA testing is right for them; and whether they have talked with their provider about PSA testing and engaged in an informed decision-making process around prostate cancer screening. **Methods**: We conducted a study among a sample of African American men patients ages $\geq$ 40 years. **Results**: A total of 65 men completed the questionnaire (response rate = 6.5%). The mean age of the men was 64.4 years. Most of the participants (90.8%) reported a regular healthcare provider and that their provider had discussed the PSA test with them (81.3%). About 84.1% of the men ever had a PSA test, but only 38.0% had one in the past year. Most of the men reported that they make the final decision about whether to have a PSA test on their own (36.5%) or after seriously considering their doctor's opinion (28.6%). About 31.8% of the men reported that they share responsibility about whether to have a PSA test with their doctor. About half of the participants (49.2%) reported that they have made a decision about whether to have a PSA test and they are not likely to change their mind. The majority of the men (75%) perceived their risk of prostate cancer to be about the same level of risk as other men who were their age. The men's knowledge of prostate cancer was fair to good (mean prostate cancer knowledge scale = 10.37, SD 1.87). Knowledge of prostate cancer was positively associated with receipt of a PSA test ($p < 0.0206$). **Conclusion**: The modest overall prostate cancer knowledge among these participants, including their risk for prostate cancer, indicates a need for prostate cancer educational interventions in this patient population.

Keywords: African Americans, men, prostate cancer, prostate specific antigen test, screening

1 Introduction

Prostate cancer is the most commonly diagnosed male cancer in the U.S. [1] African American men have the highest prostate cancer incidence rates in the world and the highest prostate cancer mortality rate of any racial/ethnic group in the U.S. [2] African American men are more likely to have locally advanced or metastatic prostate cancer at diagnosis, present at an earlier age, and have suboptimal outcomes to standard treatments [3]. African American men are 2.5 times more likely to die from prostate cancer than white men [1].

African American men are more likely to develop aggressive prostate cancer, yet less likely to be screened despite guidelines recommending shared decision-making about prostate cancer screening and PSA testing [1, 3]. It is unclear whether screening through PSA testing reduces mortality [4]. However, no firm conclusions about the benefits-to harm ratio of PSA screening can be drawn in African American men due to their limited representation in two landmark clinical trials of the effectiveness of prostate cancer screening in reducing mortality from the disease [1]. A more recent study that used Surveillance, Epidemiology, and End Results (SEER) data to investigate survival disparities between African American and white men provided a compelling case for continued PSA testing for African American men [5]. The controversy surrounding prostate cancer screening, coupled with the high rates of incidence and mortality among African American men, make it that much more important for African American men to

engage in an informed decision-making process around prostate cancer screening [6]. Previous studies have suggested that men who are more knowledgeable about prostate cancer are more likely to have been screened [7]. While informed decision-making is the current recommendation for prostate cancer screening, recent studies indicate that many African American men may not be making informed decisions about prostate cancer screening [1]. This is partly due to patients having limited knowledge of prostate cancer screening and African Americans being more likely to have inadequate health care.

We conducted a study of a sample of male, African American patients ages $\geq$ 40 years to examine predictors of prostate cancer screening. Secondary objectives were to examine whether African American men have been screened for prostate cancer; their confidence in making an informed choice about whether PSA testing is right for them; whether they have talked with their provider about PSA testing and engaged in an informed decision-making process around prostate cancer screening. We hypothesized that: H1: African American men who have more decision self-efficacy and less decisional conflict about prostate cancer screening will be more likely to have been screened; and H2: African American men who are more knowledgeable about prostate cancer will be more likely to have been screened.

2 Methods

Data are from the African American Men's Health Survey, a cross-sectional study among male, African American patients seen at Augusta University Health. Non-institutionalized men were eligible to take part in the study if they were at least 40 years of age and resided in Augusta-Richmond County or Columbia County, Georgia, or in Aiken County, South Carolina.

The patients were identified using electronic medical records. Data were collected using postal survey questionnaires. The mailings were sent to 1,000 randomly sampled potential research participants. A sequential mailing protocol was followed using a modified Dillman method [8]. An advance letter was mailed to the men by the study principal investigator (SSC). The letter provided information about the study (purpose, potential benefits, and risks). Three weeks later, a survey consent letter (Appendix) was mailed to those who had not opted out along with a copy of the survey questionnaire (Appendix) and a pre-addressed, stamped return envelope. Those who had not opted out or returned a completed questionnaire were sent a reminder postcard three weeks later.

Outcome measures: Information about prostate cancer screening was collected via postal survey. The subjects were asked: Have you ever had a PSA test? (yes / no) and whether they had a PSA test in the past year. They were also asked Do you have a regular health care provider (*e.g.*, doctor, nurse practitioner, physician assistant)? (yes / no) Has a health care provider such as a doctor or nurse ever talked to you about a PSA test? (yes / no) Questions also assessed men's self-reported levels of prostate cancer knowledge, decision self-efficacy, decisional conflict, control preferences, stage of decision making, and perceived risk related to prostate cancer screening using established reliable scales and measures [9–11]. Decisional conflict was determined by an existing 10-item Likert-type scale [9]. Stage of decision making was determined by one question with six response options to measure different stages of making a decision about the PSA test in the next 12 months, with higher values indicating greater certainty in making a decision about screening (whether to receive it or not).

Descriptive analyses and logistic regression methods were used to examine predictors of prostate cancer screening. In bivariate analyses, levels of statistical significance were determined using the one-sided Wilcoxon rank-sum test. We considered $\alpha = 0.05$ as the level of statistical significance. Levels of statistical significance were determined using Wald chi-square tests and Log-likelihood ratio tests. We present adjusted odds ratios (OR) and 95% confidence Intervals (95% CI) from logistic regression analyses. The goodness-of-fit of the model model was examined using the Log-likelihood ratio test. The study was approved by the Augusta University Institutional Review Board.

3 Results

A total of 65 men completed the study questions (response rate = 6.5%). The mean age of the men was 64.4 years (Table 1). Of the 65 surveyed participants, the majority of participants had two persons living within a household (n = 35, 59.3%), were retired (n = 28, 46.7%), were married or with partner (n = 41, 65.1%), had a HS educational level (n = 16, 25.4%), and reported good general health (n = 33, 53.4%).

Table 1 Characteristics of study participants, African American Men's Health Survey (n = 65)

Characteristic	All n (%)
Mean age (SD)* (N = 58)	64.44 (9.32)
Annual Income (N = 60)	
< $20,000	9 (15.0)
$20,000 – $34,999	4 (6.7)
$35,000 - $49,999	8 (13.3)
$50,000 - $64,999	9 (15.0)
$65,000 - $79,999	11 (18.3)
$80,000+	8 (13.3)
Missing	11 (18.3)
Number of people in household (N = 59)	
1	13 (22.0)
2	35 (59.3)
3+	11 (18.7)
Employment status (N = 60)	
Retired	28 (46.7)
Employed	10 (16.7)
On disability	16 (26.7)
Temporarily unemployed	6 (10.0)
Marital status (N = 63)	
Married/Partner	41 (65.1)
Single	12 (19.1)
Widowed	3 (4.8)
Separated/Divorced	7 (11.1)
Education (N = 63)	
Less than HS	8 (12.7)
HS or equivalent	16 (25.4)
Some college	15 (23.8)
Associate degree	7 (11.1)
Bachelor degree	9 (14.3)
Graduate degree	8 (12.7)
Perceived general health (N = 63)	
Excellent	1 (1.6)
Very good	8 (12.7)
Good	33 (52.4)
Fair	16 (25.4)
Poor	5 (7.9)

Notes: * SD: standard deviation

As shown in Table 2, most of the participants (90.8%) reported a regular healthcare provider and that their provider had discussed the PSA test with them (81.3%). About 84.1% of the men had had a PSA test, but only 38.0% had one in the past year. About one-fifth of the men (21.9%) had a positive family history of prostate cancer. Most of the men reported that they make the final decision about whether to have a PSA test on their own (36.5%) or after seriously considering their doctor's opinion (28.6%). About 31.8% of the men reported that they share responsibility about whether to have a PSA test with their doctor. About half of the participants (49.2%) reported that they have made a decision about whether to have a PSA test and they are not likely to change their mind. The majority of the men (75%) perceived their risk of prostate cancer to be about the same level of risk as other men who were their age. The men's knowledge of prostate cancer was fair to good (mean prostate cancer knowledge scale = 10.37, SD 1.87).

Additional analyzes were performed to examine factors associated with prostate cancer knowledge (results not shown). Knowledge of prostate cancer was positively associated with receipt of a PSA test ($p < 0.0206$). No significant associations were observed between decision self-efficacy or decisional conflict and receipt of a PSA test ($p > 0.05$).

When logistic regression models were fitted to the data, only one of the covariates show a significant association with the subject's history of ever taking a PSA test – the odds of the subjects taking a PSA test increase significantly when their health care provider talked about the PSA test (Table 3). The odds ratio with and without talking about the PSA test is 56.4, with a 95% confidence interval of 7.5-773.7. Among participants whose healthcare provider talked about the PSA test, 50 out of 52 (96.1%) had a PSA test. For participants whose healthcare provider never talked about a PSA test, only 3 out of 11 (27.3%) had a PSA test.

Table 2 Health characteristics and study variables among African American men seen at Augusta University Health (n = 65)

Characteristic	n (%)
Have a regular healthcare provider (N = 65)	59 (90.8)
Healthcare provider discussed PSA test (N = 64)	52 (81.3)
Ever had a PSA test (N = 63)	53 (84.1)
Had a PSA test in the past year (N = 50)	19 (38.0)
Family history of prostate cancer (N = 64)	14 (21.9)
Control preferences (N = 63)	
I make the final decision on my own	23 (36.5)
I made a decision after seriously considering my doctor's opinion	18 (28.6)
My doctor and I share responsibility for the decision	20 (31.8)
I prefer that the doctor make the decision after seriously considering my opinion	1 (1.6)
I prefer that the doctor make the decision	1 (1.6)
Stage of decision-making scale (N = 61)	
I haven't thought about it	10 (16.4)
I haven't thought about it, but I am interested in learning more	9 (14.8)
I have started to think about it, but I haven't made a decision	6 (9.8)
I have thought about it and I am close to making a decision	3 (4.9)
I have made a decision, but I am willing to reconsider	3 (4.9)
I have made a decision and I am not likely to change my mind	30 (49.2)
Perceived risk of prostate cancer scale (N = 60)	
Much lower risk	7 (11.7)
A little lower risk	7 (11.7)
About the same level of risk	45 (75.0)
A little higher risk	1 (.17)
Knowledge About Prostate Cancer	Correct Response
Most men diagnosed as having prostate cancer die of something else (N = 60)	28 (46.7)
Men are more likely to die because of prostate cancer than because of heart disease (N = 59)	45 (76.3)
It is possible to have prostate cancer if a man dos not have any symptoms (N = 60)	53 (88.3)
Prostate cancer is one of the least common cancers among men (N = 59)	42 (71.2)
If you have an abnormal PSA test result, your doctor may recommend that you have a prostate biopsy (N = 60)	56 (93.3)
The PSA test will find all prostate cancers (N = 60)	44 (73.3)
A prostate biopsy can tell you with more certainty whether you have prostate cancer than a PSA test (N = 59)	53 (89.8)
Loss of sexual function is a possible side effect of prostate cancer treatments (N = 60)	51 (85.0)
Problems with urination are possible side effects of prostate cancer treatments (N = 59)	49 (83.1)
The risk of developing prostate cancer increases with age (N = 61)	55 (90.2)
The risk of developing prostate cancer is higher in African American men as compared with men from other racial/ethnic groups (N = 56)	50 (89.3)
The risk of developing prostate cancer increases if you have a father or brother who has had prostate cancer (N = 61)	46 (75.4)
Diet rich in fruits is likely to reduce risk for developing prostate cancer (N = 60)	38 (63.3)
	Mean (SD)
Decision self-efficacy (N = 56)	38.98 (6.79)
Decisional conflict (N = 55)	33.93 (4.98)

Notes: N: the total sample. f: the frequency or correct response for Knowledge About Prostate Cancer questions (%: the relative frequency).

4 Discussion

In a survey sample among 65 African American men from the south, we observed a high prevalence (84.1%) of men that have been screened for prostate cancer. A number of reasons have been noted in the literature for the prostate cancer disparity among African American men including inadequate knowledge about prostate cancer; presentation at a later stage of prostate cancer, and more aggressive tumors in African Americans (12-14). In the current study, the majority of the participants (81.3%) reported that a health care provider such as a doctor or nurse had talked to them about a PSA test, and few of the men indicated that their health care provider had failed to encourage them to ask questions or express any concerns they had about PSA testing. Woods-Burnham *et al.* [1] found that less than half of African American men engage in conversations about prostate cancer with a healthcare provider. The U.S. Preventive Services Task Force and the American Cancer Society recommend that men engage in informed decision making with their healthcare provider after learning about the benefits and harms of prostate cancer screening [15, 16]. Potential barriers to informed decision making about PSA testing are patient-related (*e.g.*, decreased self-efficacy, fear, medical distrust) and physician-related (*e.g.*, limited availability, lack of knowledge, subpar interpersonal skills) [17]. Potential barriers to prostate cancer screening include lack of health insurance and poorer access to health care [18].

Many of the respondents in the current study had modest knowledge of prostate cancer and prostate cancer screening. Knowledge of prostate cancer has been positively associated with prostate cancer screening in some but not all studies of African American men [18, 19]. Patient's

Table 3 ORs and associated 95% CIs from univariable logistic regression models and associated p-values to examine association of different covariates with the subject taking a PSA test

Characteristic	OR (95% CI)	p-value	Overall p-value
Age (continuous)	1.03 (0.95 – 1.13)	0.491	0.491
Annual Income			
< $20,000 (Referent)	1.00		0.325
$20,000 – $34,999	1.00 (0.06 – 26.86)	1.000	
$35,000 - $49,999	2.33 (0.18 – 58.01)	0.529	
$50,000 - $64,999	Undefined	-	
$65,000 - $79,999	0.58 (0.06 – 4.19)	0.601	
$80,000+	Undefined	-	
Education			
Less than HS (Referent)	1.00		0.609
HS or equivalent	2.60 (0.26 – 27.19)	0.398	
Some college	2.60 (0.26 – 27.19)	0.398	
Associate degree	1.00 (0.09 – 11.32)	1.000	
Bachelor degree	Undefined	0.994	
Graduate degree	2.8 (0.21 – 70.84)	0.448	
History of prostate cancer in immediate family	3.00 (0.49 – 58.02)	0.307	0.307
Health care provider talked about a PSA test	66.77 (11.47 – 618.94)	< 0.001	< 0.001
Perceived risk of prostate cancer scale			
Much lower risk (Referent)	1.00		0.521
A little lower risk	Undefined	0.994	
About the same level of risk	Undefined	0.994	
A little higher risk	Undefined	1.000	
Prostate cancer knowledge scale	1.32 (0.88 – 1.99)	0.169	0.169
Decisional conflict	1.02 (0.88 – 1.21)	0.775	0.775
Decision self-efficacy	0.96 (0.82 – 1.02)	0.493	0.493

Notes: Undefined denotes estimates either with extreme/infinity values or too small.

lack of knowledge about prostate cancer and medical recommendations about prostate cancer screening may be a barrier to making an informed decision about PSA testing [19, 20]. A systematic review of 33 papers examined knowledge, awareness, and beliefs about prostate cancer and prostate cancer screening; knowledge of prostate cancer risk, symptoms, diagnostic methods and treatment options were found to contribute to greater willingness to be screened for prostate cancer [21]. Older and low-income African American study participants tend to have less knowledge about prostate cancer, risk factors, and prostate cancer screening than their white counterparts [22, 23]. In addition to younger age and higher income, greater educational attainment may be positively associated with knowledge about the prostate gland and prostate cancer screening tests [20, 24].

The three major risk factors for prostate cancer are age, race, and family history [19]. Compared to other men their age, few (1.7%) of the men in the current study perceived their risk of prostate cancer to be high or a little high. In an analysis of data from the 2003 Health Information National Trends Study, only 18% of African American men perceived themselves to be more likely to get prostate cancer than the average man of the same age, despite statistics to the contrary [25].

With respect to limitations, misclassification bias is a possibility due to the use of self-reported information. In addition, participation bias may also influence the interpretations of these results as men had to mail in their responses. Furthermore, the results of this study may not be generalizable to other populations of African American men. However, even with the limited sample size, we observed that the sample was diverse across socioeconomic factors including income and education.

In conclusion, the low overall prostate cancer knowledge among these participants, including their risk for prostate cancer, indicates a need for prostate cancer educational interventions in this patient population.

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(Edited by Snowy Wang)

Appendix

A Consent Letter

Dear xxx,

Researchers at Augusta University are conducting a health survey of African American men by mail. The survey asks questions about health status, medical history, prostate cancer screening, and smoking. It should take you about 45 minutes to complete. The results of this study will be used to obtain scientific information about the health of African American men who reside in Augusta and surrounding areas of Georgia and South Carolina. Through your participation we hope to understand the health of African American men so that prevention and treatment efforts can be improved. Results from the study will be published in scientific journals and presented at scientific conferences.

There are no known risks to you if you decide to participate in this survey other than potential, minor psychological distress. Some of the questions deal with sensitive subjects, including your physical and mental health, so we can get a more complete understanding of your health. Some people get distressed when answering these types of questions. There is no direct benefit to you for participating in this study. You will not be compensated for your participation in this research. I will not share any information that identifies you with anyone outside my research group at Augusta University.

This survey is voluntary and there is no penalty if you do not participate. It's up to you whether to answer the survey. You can skip any questions that you don't want to answer. If you do not participate, your decision will not adversely affect your relationship with Augusta University, if any. If you decide to take part in this study, you will be contacted in 4 to 5 years for a follow-up survey so that we can learn about changes in health over time. You may also receive information about additional health studies you may be eligible to participate in.

The data you provide will be stored at Augusta University. Your name and contact information will be stored separately in a locked cabinet for approximately 4 to 5 years. The data will be made available to other researchers for other studies following the completion of this research study and will not contain information that could identify you.

I hope you will take the time to complete this survey. A pre-addressed, stamped return envelope is enclosed for your convenience. If you have any questions or concerns about completing survey, about being in this study, or to receive a summary of my findings you may contact me at (706) 721-2270. If you have any questions or concerns about the "rights of research subjects", you may contact the Augusta University IRB Office at (706) 721-1483.

Sincerely,

Steven S. Coughlin, PhD
Professor of Epidemiology
Department of Population Health Sciences
Medical College of Georgia
Augusta University
1120 15th Street, AE-1042
Augusta, GA 30912

B African American men's health survey

QUESTIONNAIRE

MARKING INSTRUCTIONS

- While you can use a pen, please use a PENCIL in case you want to change an answer.
- Please do NOT use felt tip pens.
- Make solid, heavy "X" marks in the box.
- Please erase cleanly any mark you wish to change.
- Please do not make any stray marks on this form.

(This page will be kept separately from the rest of the pages to protect your privacy)

PLEASE PRINT

Name: _____ (First) _____ (Middle) _____ (Last)
Address: _____ (City) _____ (State) _____ (Zip Code)
Best telephone numbers to reach you at: (_____) _____-_____
☐ Cellular ☐ Home ☐ Work
(_____) _____-_____
☐ Cellular ☐ Home ☐ Work
Email address: _____
Before you begin the survey, please respond to the following statements.
1. I am 40 years of age or older
a. Yes
b. No
2. I live in Augusta-Richmond County or surrounding areas of Georgia or South Carolina.

a. Yes
b. No

If you answered No to either statement above, you do not need to complete the rest of the survey. Please return the survey in the postage paid envelope. We thank you for your time.

If you answered Yes to each statement above, you should complete the full survey.

PLEASE START HERE

3. In general, would you say your overall health is:
☐ 1- Excellent
☐ 2- Very good
☐ 3- Good
☐ 4- Fair
☐ 5- Poor

4. How much **bodily** pain have you had **during the past 4 weeks**:
☐ 1- None
☐ 2- Very mild
☐ 3- Mild
☐ 4- Moderate
☐ 5- Severe
☐ 6- Very Severe

5. For how long (if at all) has your **health limited you** in **each** of the following activities?

	Limited for more than 3 months	Limited for 3 months or less	Not limited at all
a. The kinds or amounts or vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports	0 – 1	0 – 2	0 – 3
b. The kind or amounts of moderate activities you can do, like moving a table, carrying groceries, or bowling	0 – 1	0 – 2	0 – 3
c. Walking uphill or climbing a few flights of stairs	0 – 1	0 – 2	0 – 3
d. Bending, lifting, or stooping	0 – 1	0 – 2	0 – 3
e. Walking one block	0 – 1	0 – 2	0 – 3
f. Eating, dressing, bathing, or using the toilet	0 – 1	0 – 2	0 – 3

6. Does your health **keep** you from working at a job, doing work around the house, or going to school?
☐ 1- YES, for more than 3 months
☐ 2- YES, for 3 months or less
☐ 3- NO

7. Have you been unable to do **certain kinds or amounts** of work, housework, or schoolwork because of your health?
☐ 1- YES, for more than 3 months
☐ 2- YES, for 3 months or less
☐ 3- NO

For **each** of the following questions, please mark the circle for the **one** answer that comes **closest** to the way you have been feeling **during the past month**.

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
8. How much of the time, during the past month, has your **health limited your social activities** (like visiting with friends or close relatives)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
9. How much of the time, during the past month, have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. During the past month, how much of the time have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. How much of the time, during the past month, have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. During the past month, how much of the time have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. How often, during the past month, have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

14. Please mark the square that best describes whether **each** of the following statements is true or false for you.

	Definitely true	Mostly true	Not sure	Mostly false
a. I am somewhat ill	☐ 1	☐ 2	☐ 3	☐ 4
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4
c. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4
d. I have been feeling bad lately	☐ 1	☐ 2	☐ 3	☐ 4

15. Do you drink alcohol on a regular basis (irrespective of amount of alcohol consumed)?
a. Yes
b. No
c. Prefer not to answer

HEALTH INFORMATION

Please mark an X beside each of the health conditions that you discussed with a healthcare provider and indicate the date (month/year) it was first noted.

☐ High blood pressure
☐ High cholesterol
☐ Stomach problem
☐ Lung/breathing problem
☐ Rheumatoid arthritis
☐ Congestive heart failure
☐ Heart attack
☐ Stroke
☐ Chronic bronchitis
☐ Emphysema
☐ Asthma
☐ Bladder/kidney problem
☐ Depression
☐ Anxiety
☐ Diabetes/sugar problem
☐ Osteoporosis
☐ Cancer (Specify type) _____
☐ Other _____

Are you currently taking medications for any of the conditions below? Please CHECK ALL that apply

☐ Diabetes
☐ High blood pressure
☐ High cholesterol
☐ Other (Please specify)_____

Do you have any other condition or illness that was not checked above?
If so, what is it? _____

PROSTATE CANCER SCREENING

16. Have you ever heard of a PSA or prostate-specific antigen test?
a) yes
b) no
17. Have you ever had a PSA test?
a) yes
b) no (**skip to 19**)
18. When did you have your most recent PSA test?
a) a year ago or less
b) more than 1 but not more than 2 years ago
c) more than 2 but not more than 5 years ago
d) over 5 years ago

The next few questions are about discussions that health care providers might have had with you about the PSA test.

19. Do you have a regular health care provider (e.g., doctor, nurse practitioner, PA)?
a) yes
b) no
20. Has a health care provider such as a doctor or nurse ever talked to you about a PSA test?
a) yes
b) no (**skip to 23**)
21. Thinking about the last time a health care provider talked to you about a PSA test, which of the following statements best describes your health care provider's recommendation about PSA tests?
a) that you should have a PSA test
b) that you should not have a PSA test
c) your health care provider did not make a recommendation
22. Thinking about the last time a health care provider talked to you about a PSA test, did your health care provider encourage you to ask questions or express any concerns you had about PSA testing? Would you say . . .
a) yes, definitely
b) yes, somewhat, or
c) no, not at all
d) DID NOT HAVE ANY QUESTIONS OR CONCERNS ABOUT PSA

My Confidence in making an informed choice **Decision Self-Efficacy Scale**

Below are listed some things involved in making an informed choice. Please show how confident you feel in doing these things by circling the number from 0 (not at all confident about PSA testing or not getting it) to 4 (very confident) for each item below.

I feel confident that I can:

23. Get the facts about the prostate cancer screening decisions choices available to me	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
24. Get the facts about the benefits of each choic	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
25. Get the facts about the risks and side effects of each choice, whether or not to get prostate cancer screening	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
26. Understand the information enough to be able to make a choice	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
27. Ask questions without feeling dumb	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
28. Express my concerns about each choice	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
29. Ask for advice	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
30. Figure out the choice that best suits me	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
31. Handle unwanted pressure from others in making my choice	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
32. Let my healthcare provider know what's best for me	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident
33. Delay my decision if I feel I need more time	Not at all confident	Somewhat not confident	Neutral	Somewhat confident	Very confident

Please answer the following questions about how confident you are about making an informed decision about prostate cancer screening: ***Decisional Conflict Scale***

34. I'm aware of the choices I have for prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree
35. I feel I know the benefits of prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree
36. I feel I know the risks and side effects of prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree
37. I know how important the benefits are for prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree
38. I am clear about which risks and side effects matter most to me for prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree
39. I have enough support from others to make a choice.	Strongly disagree	Disagree	Agree	Strongly agree
40. I choose without pressure from others.	Strongly disagree	Disagree	Agree	Strongly agree
41. I have enough advice to make an informed choice.	Strongly disagree	Disagree	Agree	Strongly agree
42. I am satisfied with my decision.	Strongly disagree	Disagree	Agree	Strongly agree
43. I expect to stick with my decision.	Strongly disagree	Disagree	Agree	Strongly agree

We are interested in how satisfied you are with your decision about prostate cancer screening. Please indicate how much you agree or disagree with the following statements ***Satisfaction with Decision Scale (post-test only)***

44. I am satisfied that I was adequately informed about the issues important to my decision about screening for prostate cancer.	Strongly disagree	Disagree	Agree	Strongly agree
45. The decision I made about prostate cancer screening was the best decision possible for me personally.	Strongly disagree	Disagree	Agree	Strongly agree
46. I am satisfied that my decision about prostate cancer screening was consistent with my personal values.	Strongly disagree	Disagree	Agree	Strongly agree
47. I expect to continue to carry out the decision I made about prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree
48. I am satisfied that this was my decision to make.	Strongly disagree	Disagree	Agree	Strongly agree
49. I am satisfied with my decision about prostate cancer screening.	Strongly disagree	Disagree	Agree	Strongly agree

50. Who should make medical decisions? **Control Preferences Scale**
a) I make the final decision on my own
b) I made a decision after seriously considering my doctor's opinion
c) My doctor and I share responsibility for the decision
d) I prefer that the doctor make the decision after seriously considering my opinion
e) I prefer that the doctor make the decision
51. When you think about getting a PSA test in the next 12 months, which sentence best describes you? **Stage of Decision Making Scale**
a) I haven't thought about it
b) I haven't thought about it, but I am interested in learning more
c) I have started to think about it, but I haven't made a decision
d) I have thought about it and I am close to making a decision
e) I have made a decision, but I am willing to reconsider
f) I have made a decision and I am not likely to change my mind

52. What do you think is your risk of developing prostate cancer compared to other men your age?

Perceived Risk of Prostate Cancer Scale a) Much lower risk
b) A little lower risk
c) About the same level of risk
d) A little higher risk
e) Much higher risk

My Knowledge about Prostate Cancer **Prostate Cancer Knowledge Scale**

53. Most men diagnosed as having prostate cancer die of something else _____
54. Men are more likely to die because of prostate cancer than because of heart disease _____
55. It is possible to have prostate cancer if a man does not have any symptoms _____
56. Prostate cancer is one of the least common cancers among men _____
57. If you have an abnormal PSA test result, your doctor may recommend that you have a prostate biopsy _____
58. The PSA test will find all prostate cancers _____
59. A prostate biopsy can tell you with more certainty whether you have prostate cancer than a PSA test _____
60. Loss of sexual function is a possible side effect of prostate cancer treatments _____
61. Problems with urination are possible side effects of prostate cancer treatments _____
62. The risk of developing prostate cancer increases with age _____
63. The risk of developing prostate cancer is higher in African American men as compared with men from other racial/ethnic groups _____
64. The risk of developing prostate cancer increases if you have a father or brother who has had prostate cancer _____
65. Diet rich in fruits is likely to reduce risk for developing prostate cancer _____
66. Do you have a history of prostate cancer in your immediate family (such as a father, brother)?
a) yes
b) no
67. What is your height? (please enter your height in feet and inches)
_____ _____ _____
Q68. How much do you weigh? (Please enter your weight in pounds)
_____ _____ _____
Q69. How do you describe your weight? (Circle correct answer)
a. Very underweight
b. Slightly underweight
c. About the right weight
d. Slightly overweight
e. Very overweight
f. Prefer not to answer
Q70. Which are the following are you trying to do about your weight? (Circle correct answer)
a. Lose weight
b. Stay the same
c. Gain weight
d. Not trying to do anything about my weight
e. Prefer not to answer

TOBACCO USE

Q71. Have you ever smoked a cigarette?
a. Yes
b. No
Q72. If answered yes on Q71, Have you smoked 100 cigarettes (5 packs) in your lifetime?
c. Yes
d. No
Q73. If answered yes on Q71. Do you now smoke cigarettes?
a. Every day
c. Some days
d. Not at all
Q74. If answered yes on Q71. How old were you the first time you smoked part or all of a cigarette?
OR
Q74. If answered yes on Q71. How old were you when you first started smoking fairly regularly?
Q75. How many cigarettes smoked per day when you smoked fairly regularly _____
Q.76. [On the days that you smoke] How soon after you wake up do you typically smoke your first cigarette of the day? Please enter the number of minutes or hours _____
Q.77. In the past 12 months, how many times have you stopped smoking for one day or longer because you were trying to quit?
a. 0 times
b. 1 time
c. 2-3 times
d. 4 or more times
Q78. When do you plan to quit smoking for good?
a. In the next 7 days
b. In the next 30 days
c. In the next 6 months
d. In the next year

e. More than one year from now
f. I never plan to quit smoking

E-cigarette use

Q79. Have you ever used Vaporizers, E-Cigarettes, and other Electronic Nicotine Delivery Systems (ENDS) some brand examples include JUUL, NJOY, Blu, Vuse, MarkTen, Logic, Vapin Plus, eGo, Halo, GreenSmoke, Fin, and KangerTech.
Yes
No
Q80. Have you ever used Vaporizers, E-Cigarettes, and other ENDS fairly regularly?
Yes
No
Q81. Do you now use Vaporizers, E-Cigarettes, and other ENDS?
Everyday
Somedays
Not at all
Q82. Have you ever smoked little filtered cigars or cigarillos, some brand names include Black and Mild, White Owl, and Swisher Sweets?
Yes
No
Q83. Have you ever smoked little filtered cigars or cigarillos, some brand names include Black and Mild, White Owl, and Swisher Sweets fairly regularly?
Yes
No
Q84. Do you now smoke little filtered cigars or cigarillos, some brand names include Black and Mild, White Owl, and Swisher Sweets?
Everyday
Somedays
Not at all
Q85. Have you ever used Smokeless Tobacco Products, Including Dip, Snuff, Snus, and Chewing Tobacco?
Yes
No
Q86. Have you ever used Smokeless Tobacco Products, Including Dip, Snuff, Snus, and Chewing Tobacco fairly regularly?
Yes
No
Q87. Do you now use Smokeless Tobacco Products, Including Dip, Snuff, Snus, and Chewing Tobacco?
Everyday
Someday
Not at all
E-cigarettes/ENDS are considered tobacco products by the FDA because most of them contain nicotine, which comes from tobacco. There are increasing concerns about the health risks associated with use of e-cigarettes/ENDS. You can find out more about these issues by clicking on the Advisory on E-Cigarette Use among Youth issued by the U.S. Surgeon General, and the Severe Pulmonary Disease Associated with Using E-Cigarette products issued by the Centers for Disease Control & Prevention (CDC).

DEMOGRAPHICS

88. Age: _____ years
89. Race/Ethnicity
a) African American
b) Afro-Caribbean
c) Afro-Haitian
d) Afro-Hispanic
e) African
f) Other
90. Marital status:
a. Single
b. Married
c. Partner
d. Separated
e. Divorced
f. Widowed
g. I choose not to answer
91. Education
f. Less than High School degree
g. High School Degree or equivalent (e.g., GED)
h. Some College but no degree
i. Associate Degree
j. Bachelor Degree
k. Graduate Degree
l. I choose not to answer
92. Annual household income

m. < $20,000
n. $20,000 - $34,999
o. $35,000 - $49,999
p. $50,000 - $64,999
q. $65,000 - $79,999
r. $80,000 to $99,00
s. $100,000 or more
t. I choose not to answer
u. I don't know
93. Number of people in household: _____
94. Employment status:
v. Temporarily unemployed
w. Employed (> 20 hours / week)
x. Homemaker
y. On disability
z. Retired

That's all the questions we have for you. Thank you for your time.

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RESEARCH ARTICLE

Individual prostate cancer screening: Practice survey with general practitioner of Lubumbashi, Democratic Republic of Congo

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Abstract: **Objective**: To analyze the practices of general practitioners (GPs) in terms of recommendations on individual screening for prostate cancer (PCa). **Methods**: An anonymous cross-sectional survey using a pre-established questionnaire was conducted among 193 GPs in the city of Lubumbashi from May 1st to July 31st, 2020. The questionnaire included three parts: identity criteria of GPs, screening practice and the opinion of GPs on the recommendations. **Results**: The participation rate was 79%. Eighty-two-point nine percent of respondents said they offered screening for PCa; 42.5% of them said they offered this screening to all men within a certain age limit, ranging between 50 to 75 years in 38.8% of the cases. Only 12.5% of GPs provided complete prior information to their patients. Thirty-six-point three percent of GPs reported combining digital rectal examination with total PSA testing, but in the presence of an abnormality, 60.6% reported that they referred their patients directly to the urologist without ordering other additional investigations (first or second line). Finally, 32.7% of GPs found that the recommendations disseminated were appropriate for their practice. **Conclusion**: Individual screening for PCa is widely proposed; but there are differences between the practices reported by GPs and official recommendations of learned societies. Our study highlights the need to popularize the recommendations of learned societies to GPs.

Keywords: prostate cancer, individual screening, general practitioner

1 Introduction

Prostate cancer (PCa) is the most common cancer in men. It is therefore a public health problem and has become a major concern for men from their fifties [1]. A recent study conducted in Lubumbashi by Mbey *et al*. [1] reported a 3-year overall survival rate of 56.82%. They found that there is a statistically significant correlation between the appearance of PCa on digital rectal examination, PSA level and patients' outcome [1].

PCa screening has even been the subject of much controversy as to its merits. Previous studies have reported the existence of the risk of over-diagnosis and over-treatment of PCa by performing prostate-specific antigen (PSA) screening [2,3]. Mass screening for PCa is currently controversial around the world. On the other hand, several learned societies recommend individual screening after providing appropriate and informed information to men on the following points: (i) the natural history of PCa and its risk factors; (ii) description and performance of diagnostic tests; (iii) uncertainty in reducing mortality individual PCa screening, as well as (iv) existing therapeutic options, their benefits and side effects [4]. Pending a possible organized screening is in place, the general practitioner (GP), as the manager of primary care remains as the central player in the recommendation of individual PCa screening. He is the first to face the request for information and who must make the decision whether or not to take this step, in agreement with his patient. The importance of the role of GPs in screening for certain cancers has been widely demonstrated by several authors [5–7]. The contribution of GPs remains important in recommending patients for individual PCa screening [7]. In our community, the recommendations of learned societies on the individual screening approach are not popularized.

Noting the importance of the GP in this diagnostic approach, it seemed interesting to us to make an "inventory" of the practices of GPs in relation to the PCa screening in Lubumbashi.

2 Materials and methods

This is a cross-sectional study carried out from May 1 to July 31, 2020 among GPs practicing in private clinics, health centers and, general referral hospitals in the city of Lubumbashi in the Haut-Katanga province in Democratic Republic of Congo.

Participants in the study had voluntarily signed and received a structured questionnaire and self-administered, with an explanatory note on the purpose of the study. Data were collected using a standardized self-administered questionnaire, addressed to concerned. We used to model the questionnaire used by Guy *et al*. [6] (Supplementary material). In their study, which included 18 questions. Questions 1 to 7 concerned the identity criteria of GPs. The 8 to 17 concerned the screening itself: the population screened, information on the various aspects of screening, screening tools, the actions to be taken after positive and negative screening. Question 18 asked for the opinion of GPs on the recommendations. Concerning the information given to patients, we chose to interview GPs on four types of information they gave to their patients:

(1) the natural history of PCa and its risk factors;

(2) treatment options;

(3) screening tests and the uncertainty of the reduction in mortality;

(4) the continuation of the investigations if the screening was positive.

The encoding, processing and statistical analysis of the data were performed with STATA software version 15. The information from the survey was summarized using descriptive statistics. Information of the quantitative type was represented in the form of mean and standard deviation, while that of qualitative type in the form of counts and percentages.

Inferential statistics were used to compare variables. Unpaired *t*-test was performed to compare the age of respondents depending on whether or not they offered individual PCa screening. Of the latter variable, the comparison of proportions by sex, exercise setting, mode of exercise, and type of health facility was performed using Fisher's exact test. A significance level of 5% was retained and for a two-tailed test with a value of $p < 0.05$ was considered significant.

3 Results

Of 244 GPs surveyed, 193 had agreed to answer the questionnaire, which corresponds to a participation rate of 79%. All questionnaires were exploitable:

(1) One hundred and sixty (82.9%) GPs who responded to this questionnaire declared that they offered individual PCa screening;

(2) Thirty-three (17.1%) GPs responded that they did not perform PCa screening.

We observed no significant difference ($p > 0.05$) between the two physician groups regarding mean age, sex, mode of exercise, practice environment, and health facility (other results are summarized in Table 1).

Table 1 General characteristics of the study population

Variable	Do you offer individual prostate cancer screening?		Total	p-value
	No (n = 33)	Yes (n = 160)	N = 193	
Age (*mean* ± *SD*)	37.1 ± 6.5	37.4 ± 5.8	37.3 ± 5.9	0.7948
Sex				0.1927
Female	12 (23.5%)	39 (76.5%)	51	
Male	21 (14.8%)	121 (85.2%)	142	
Practice settings				0.7909
Semi-rural	4 (13.8%)	25 (86.2%)	29	
Urban	29 (17.7%)	135 (82.3%)	164	
Practice mode				0.4081
Group practice	21 (15.6%)	114 (84.4%)	135	
Individual practice	12 (20.7%)	46 (79.3%)	58	
Health facility				1.000
Private	16 (17.6%)	75 (82.4%)	91	
Public	17 (16.7%)	85 (83.3%)	102	

The following results relate only to the 160 GPs who declared that they offered screening.

(A) *Target population for PCa screening*

Among the GPs who said they offered screening, 66.9% said they offered it to men with functional urinary disorders and 42.5% said they offered it to all men within a certain age limit. In 38.8% of cases, it ranged from 50 to 75 years and in 55.6% of cases the lower limit began at 45 years.

(B) *Information to give to patients*

The results regarding the information given to the patients are reported in Table 2. Only 20 (12.5%) GPs provided all the information (regarding all the data) before initiating screening. Instead, information on the natural history of PCa and risk factors, as well as screening investigations, was given before they were done.

Information on treatment options and that on further investigations were rather data after running the tests.

Table 2 Distribution of respondents based on the information provided

Time of issue	Information type			
	Information on natural history of cancer and its risk factors (%)	Information about treatment options (%)	Information on screening tests and uncertainty of mortality reduction (%)	Information on further investigations if screening positive (%)
Before screening	59.38%	31.25%	47.50%	26.25%
After screening	17.50%	42.50%	11.88%	54.38%
Not given	23.13%	26.25%	40.63%	19.38%

(C) *PCa screening tools*

Among the GPs who said they offered screening:

(1) 36.3% declared that they only used digital rectal examination combined with the total serum PSA assay;

(2) 29.4% declared using the digital rectal examination combined with the total serum PSA assay, in combination with other complementary investigations;

(3) 16.3% used digital rectal examination alone without doing a total serum PSA assay;

(4) 8.8% declared that they used other tools, such as free PSA testing and / or endorectal ultrasound of the prostate, as a first-line treatment.

(D) *What to do in the event of a positive PCa screening*

Among the GPs who said they offered screening:

(1) 60.6% declared to send directly to the urologist the patients whose screening tests were suspicious (in the event of an abnormality in the digital rectal examination and / or total serum PSA assay) without performing other additional investigations;

(2) 22.5% said they actually referred their patients to the urologist and also performed other investigations;

(3) Finally, 16.9% declared that they were continuing the diagnostic process themselves, by ordering other additional investigations (endorectal ultrasound of the prostate, the determination of free PSA and its ratio to total PSA, and control of total serum PSA).

(E) *What to do if PCa screening is negative*

Among the GPs who said they offered screening:

(1) 60.6% declared to send patients directly to the urologist even if the screening was negative without performing other additional examinations;

(2) 23.1% said they checked the digital rectal examination and the total serum PSA assay more than once a year;

(3) 13.8% declared that they checked the digital rectal examination and the total serum PSA assay once a year, or even less often.

(F) *Opinion of GPs on recommendations*

GPs offering PCa screening estimated 32.7% that the recommendations were appropriate for their office practice and 67.3% believed that they were not.

4 Discussion

This is the first study conducted in Lubumbashi among GPs to analyze their practices in relation to individual PCa screening. It demonstrated a majority support for the principle of PCa screening in the population of GPs studied. The need for PCa screening seems perfectly accepted by GPs in Lubumbashi since the majority of them (82.9%) offered it to their patients. However, there were significant differences in their existing practices and recommendations. The results of our survey were lower than those of Guy *et al*. [6] who report that 98.3% of French GPs declared performing individual screening for this cancer. The dissimilarity of

our results with those of French authors would be linked to the codification and follow-up of recommendations by French GPs, unlike Congolese GPs where these recommendations are not popularized to them. In our study, the majority of GPs reported offering screening to all men (42.5%) in the age group of 50 to 75 years (38.8%). In 55.6% of cases, the lower limit beginning at age 45. The study by Guy *et al*. [6] found that 89.5% of surveyed French GPs reported offering screening to all men and 80.8% in the age group of 50 to 75 years. Studies in other countries show that GPs often offered PSA test under varying circumstances in asymptomatic patients [8], during a "check-up" medical [9, 10], or the patient's request [11].

In our survey, 65.7% of the GPs prescribed a PSA test combined with a digital rectal exam. This rate is lower than that observed in several other countries [7–10]. Learned societies and health authorities, they recommend or not the individual PCa screening, advise regulate this practice by clear information before the patient to initiate screening. Our survey showed a certain deficit in the provision of information by GPs, with a low rate of GPs (12.5%) who declared that they provided the four types of information (natural history, screening tests, uncertainty about the reduction in mortality, therapeutic options) before starting the diagnostic process. The least information given was that concerning treatment options and further investigation in case of positive screening. The same information was given mostly too late, that is to say after receiving the test results. Results from other studies [6, 12, 13] confirm that information on the benefits, limitations and consequences of PSA testing is lacking.

The results of our study also show uncertainty in the identification and use of screening tools, as well as in what to do in the event of a positive screening. In fact, only 36.3% of the GPs declared that they performed first-line digital rectal examination and total serum PSA assay. It also appears that the GPs in our study declared that they used additional investigations that were not recommended (endorectal ultrasound, free PSA assay) as first (8.8%) or second-line (16.9%). This reinforces the idea that good practice guides are needed to be developed in the field of prostatic pathology.

Our study has allowed us to better understand physician practices which will allow a better definition of training needs for better integration into the national cancer screening program. The GP is not only one that treats the disease but also one that takes care of patients by providing all preventive measures. It is in this perspective that prevention and screening are essential. The results of European and American studies represented an important step in understanding the benefits of PCa screening impacting on specific mortality (reduction of approximately 2% per year in PCa mortality) [2, 3]. This is related to the improvement of diagnostics and advances in care. Finally, they are part of the logic of establishing an early curative treatment for this cancer. The PCa screening becomes an imperative in African environment where it is often found in advanced stages and not curative. Thus, the earlier the diagnosis is made at an early stage and asymptomatic, the greater the chances of cures for patients. This involves the role and responsibility of GPs on better use of the currently available investigations. Although this is declarative data, several highlights are highlighted by this study. It shows that GPs are aware of being very involved in prevention measures in their daily practice. It should be noted the methodological limitations of this type of study. Indeed, bias risk is related to respondents, probably more invested in prevention measures that non-respondents. Moreover, the data we have obtained are unverified because they are declarative data; it is likely, as has already been shown that there is a gap between what the doctor says and do what he does in reality [14]. However, our results confirm those of other studies, thereby suggesting that the information we have collected are valid and interpretable.

5 Conclusion

Our study has shown that in our community, individual PCa screening is regularly carried out in general medicine. However, information available to GPs, facing a population often insufficiently informed, seem incomplete. It is also noted a large prescription for additional examinations, resulting from a poor identification of screening tools. Individual PCa screening is massively offered by GPs, but differences are observed between their reported practices and official guidelines. Our study highlights the need to provide patients with clear and comprehensive information by improving knowledge of GPs through continuing education regarding the PCa screening and the use of the algorithm that we propose them (Figure 1).

Competing interests

The authors declare that they have no competing interests.

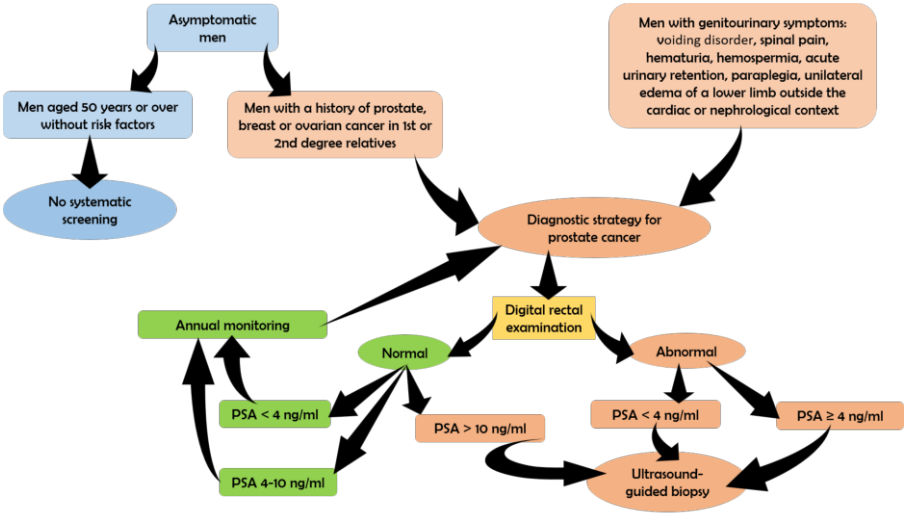

Figure 1 Algorithm for prostate cancer screening in limited resource settings

Authors' contributions

All authors participated in the development and conduct of this study, and all have read and approved the final version of the manuscript.

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RESEARCH ARTICLE

Problems in living among breast cancer survivors

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Abstract: **Purpose**: Breast cancer survivors may experience worse social, physical, and emotional function compared to the general population, although symptoms often improve over time. Data on problems in living can help to improve interventions and supportive care for breast cancer survivors. Symptoms such as fatigue, pain, difficulties with sleep, and sexual problems may have an adverse effect on the quality of life of breast cancer survivors. **Methods**: We examined problems in living using data from a survey of 164 breast cancer survivors who had completed primary therapy for the disease. **Results**: A total of 164 women completed the study questions (response rate 16.4%). The mean age of the women was 67 years. Among all participants, 66.7% were white, 29.5% were African-American, and the remainder were of other races. Almost all of the symptoms were more likely to be reported by participants who were $<$ 55 years of age. Other important correlates of symptoms included non-white race, marital status, and having a household income of less than $50,000 per year. **Conclusion**: The results of this study highlight the need for caregivers to emphasize screening for and discussion of symptoms, including sleep difficulties, fatigue, loss of strength, aches and pains, and muscle or joint stiffness. Of particular concern are younger survivors and those who are African American or low-income.

Keywords: breast cancer, cancer survivors, problems

1 Introduction

In the United States, an estimated 3.8 million women have a history of invasive breast cancer [1]. Improvements in survival rates due to earlier detection and improvements in therapy have led to new challenges related to the quality of survivorship [2]. Previous studies indicate that breast cancer survivors may experience worse social, physical, and emotional function compared to the general population, although symptoms often improve over time [3–5]. Commonly reported symptoms include sleep difficulties, fatigue, pain, cognitive problems, sexual issues, and hot flashes [6]. Such symptoms may have an adverse effect on the quality of life of breast cancer survivors [2]. Frequently, they are due to the therapy received. For example, arthralgias are a frequent side-effect of aromatase inhibitors, which are frequently used for the treatment of postmenopausal women with hormone-receptor-positive breast cancer [6]. Patients who underwent mastectomy or axillary dissection may experience persistent pain at the surgical site or lymphedema in the affected extremity [2]. Data on problems in living can help to raise awareness among patients and physicians, to improve detection, and to design interventions and supportive care for breast cancer survivors.

We thus examined problems in living using data from a survey of 164 breast cancer survivors who had completed primary therapy for their breast cancer. The overall objective was to determine the prevalence and correlates of symptoms and other problems in living.

2 Methods

The Cardiovascular Disease outcomes among Breast Cancer Survivors Study (CVDBCS) was a postal survey of a multiethnic cohort of breast cancer survivors who reside in Augusta, GA and who had been treated at Augusta University Health and/or the Georgia Cancer Center. Non-institutionalized women were eligible to take part in the study if they resided in Augusta-Richmond County and Columbia County, GA, or in Aiken County, SC, had been diagnosed

with stage I-IV breast cancer, and had completed primary therapy for the disease other than hormonals.

Data were collected using postal survey questionnaires and via abstraction of electronic medical records. The mailings were sent to 1,000 potential research participants who were randomly sampled. A sequential mailing protocol was followed using a modified Dillman method [7]. An advance letter was mailed to the women by the study principal investigator (S.S.C.). The letter provided information about the study (purpose, potential benefits, and risks) and clearly informed patients that they could opt out and not receive further mailings about the study. Three weeks later, a survey consent letter was mailed to women who had not opted out along with a copy of the survey questionnaire and a pre-addressed, stamped return envelope. Women who had not opted out but had not returned a completed questionnaire after 4 weeks of the initial mailing were sent a reminder postcard. Survey responses were checked for completeness and then coded and entered into an electronic database. Questions about demographic factors and breast cancer diagnosis were obtained from a previous study of breast cancer survivors. Respondents were asked about their physical, psychological, and social functioning using the Cancer Problems in Living Scale (CPILS) [8]. The version of the CPILS used in this study was expanded from 31 items to include 50 CPILS items [9]. All of the CPILS items use a three-point Likert-like response scale, with response options being: 0 = not a problem, 1 = somewhat of a problem, and 2 = a severe problem.

After crosstabulations and exploratory analyses of the survey data were completed, logistic regression methods were used to compare groups of breast cancer survivors who did or did not report individual symptoms according to age, race, marital status, and household income. The dependent variable in these analyses was whether or not the respondent indicated that the symptom was "somewhat of a problem" or "a severe problem." Ninety-five percent confidence intervals (CIs) were obtained for adjusted odds ratios (ORs). Levels of statistical significance were determined using Wald chi-square tests. The goodness-of-fit of each model was examined using the Log-likelihood ratio test.

Another measure of interest we considered is the total number of problems that participants considered as somewhat of a problem or a severe problem. Across the 40 questions asked, the total number of responses with a value of 1 or 2 were recorded. A multivariate Poisson regression model was then fit to identify the association of this score with various factors such as age, race, household income, marital status, *etc*.

3 Results

A total of 164 women completed the study questions (response rate 16.4%). The mean age of the women was 67 years (Table 1). Among all participants, 66.7% were white, 29.5% were African-American, and the remainder were of other races. More than half (58.4%) of the women were insured through Medicare and 29.2% held private insurance. The remainder had Medicaid or were uninsured. With respect to breast cancer stage at diagnosis, 19.8% of the women had ductal carcinoma in situ, 26.8% had stage I disease, 21.0% had stage II disease, 8.9% had stage II disease, and 5.1% had stage IV disease. The mean number of years since diagnosis was 9.4 years. About 54.9% of the women reported receiving chemotherapy and only 4.9% reported biologic/targeted therapy.

Problems in living reported by the study participants are shown in Table 2. Symptoms reported by at least 50% of the participants as "somewhat a problem" or "a severe problem" combined included sleep difficulties (53%), fatigue (56%), loss of strength (59%), forgetfulness (57%), aches and pains (71%), and muscle or joint stiffness (67%). Several symptoms were reported as a severe problem by at least 15% of the participants including fatigue (16%), loss of strength (18%), aches and pains (21%), muscle or joint stiffness (17%), dryness in vagina (15%), less sexual desire (23%), and hot flashes (17%).

Almost all of the symptoms were more likely to be reported by participants who were less than 55 years of age (Table 3). Other important correlates of symptoms included non-white race (Table 4), marital status (Table 5), and having a household income of less than $50,000 per year (Table 6). Compared to those who were not married/living with a partner, participants who were married or living with a partner were more likely to report sexual problems, but less likely to report signs of financial distress (Table 5). Lower income participants were more likely to report having major problems with their health and signs of financial distress (Table 6).

For the total score on problems reported as somewhat of a problem/a severe problem, there was a significant relationship between the total score on issues reported as somewhat/severe problem and age (decreasing with age), race (higher for non-whites *vs.* whites), marital status (higher for married women *vs.* non-married women), total household income (higher for

Table 1 Characteristics of study participants (n = 164)

Characteristic	Frequency (%)
Age (years) mean (SD) (N = 163)	67 (41.1)
Race (N = 156)	
White, Non-Hispanic	104 (66.7)
African American, Non-Hispanic	46 (29.5)
Other	6 (3.9)
Annual Income (N = 46)	
<$20,000	17 (10.4)
$20,000-$34,999	17 (10.4)
$35,000-$49,999	17 (10.4)
$50,000-$64,999	14 (8.5)
$65,000-$79,999	8 (4.9)
$80,000 +	38 (23.2)
Missing	53 (32.3)
Number of people in household (N = 160)	
1	48 (30.0)
2	83 (51.9)
3 +	29 (18.1)
Employment status (N = 163)	
Retired	99 (60.7)
Employed	34 (20.9)
On disability	16 (9.8)
Homemaker	9 (5.5)
Temporarily unemployed	4 (2.5)
Marital status (N = 163)	
Married/Partner	84 (51.5)
Single	24 (14.7)
Widowed	32 (19.6)
Separated/Divorced	23 (14.1)
Education (N = 157)	
Less than HS	5 (3.2)
HS or equivalent	42 (26.8)
Some college	27 (17.2)
Associate degree	22 (14.0)
Bachelor degree	27 (17.2)
Graduate degree	34 (21.7)
Health Insurance (N = 161)	
Medicare	94 (58.4)
Private insurance	47 (29.2)
Other	20 (12.4)
Perceived general health (N = 162)	
Excellent	16 (9.9)
Very good	58 (35.8)
Good	59 (36.4)
Fair	24 (14.8)
Poor	5 (3.1)
Breast cancer stage at diagnosis (N = 157)	
Ductal carcinoma in situ	31 (19.8)
Stage I	42 (26.8)
Stage II	33 (21.0)
Stage III	14 (8.9)
Stage IV	8 (5.1)
Don't know	29 (18.5)
Time since diagnosis (in years) mean (SD) (N = 155)	9.4 (8.8)
Type of treatment received(N = 164)	
None	2 (1.2)
Surgery	161 (98.2)
Radiation	111 (67.7)
Chemotherapy	90 (54.9)
Hormone therapy	74 (45.1)
Biologic/Targeted therapy	8 (4.9)

Table 2 Problems in living reported by study participants (n = 164)

Description	Total responses	Not a problem N (%)	Somewhat of a problem N (%)	A severe problem N (%)
Sleep difficulties	156	74(47.44)	64(41.03)	18(11.54)
Fatigue	158	69(43.67)	64(40.51)	25(15.82)
Loss of Strength	157	64(40.76)	65(41.40)	28(17.83)
Preoccupation with being ill	154	106(68.83)	37(24.03)	11(7.14)
Major problems with my health	157	100(63.69)	40(25.48)	17(10.83)
Trouble concentrating	152	92(60.53)	47(30.92)	13(8.55)
Being physically unable to have children	138	128(92.75)	3(2.17)	7(5.07)
Being physically unable to have sexual intercourse	151	110(72.85)	31(20.53)	10(6.62)
Forgetfulness	155	66(42.58)	70(45.16)	19(12.26)
Aches and pains	157	45(28.66)	79(50.32)	33(21.02)
Tenderness at surgical site	157	95(60.51)	51(32.48)	11(7.01)
Muscle or joint stiffness	155	51(32.90)	78(50.32)	26(16.77)
Arm swelling	154	126(81.82)	19(12.34)	9(5.84)
Dryness in vagina	153	81(52.94)	49(32.03)	23(15.03)
Pain during sexual intercourse	144	91(63.19)	35(24.31)	18(12.50)
Less sexual desire	148	79(53.38)	35(23.65)	34(22.97)
Hot flashes	151	80(52.98)	46(30.46)	25(16.56)
Sweating	153	84(54.90)	47(30.72)	22(14.38)
Feeling fearful that my illness will return	155	90(58.06)	47(30.32)	18(11.61)
Fears about the future	154	99(64.29)	37(24.03)	18(11.69)
Having difficulty in making long-term plans	154	117(75.97)	26(16.88)	11(7.14)
Feeling emotionally vulnerable	155	116(74.84)	28(18.06)	11(7.10)
Feeling helpless	157	125(79.62)	25(15.92)	7(4.46)
Feeling angry	156	122(78.21)	27(17.31)	7(4.49)
Feeling dependent	156	116(74.36)	27(17.31)	13(8.33)
Feeling isolated	155	124(80.00)	22(14.19)	9(5.81)
Guilt feelings	155	138(89.03)	11(7.10)	6(3.87)
Feeling sad	156	113(72.44)	37(23.72)	6(3.85)
Feeling anxious	156	99(63.46)	45(28.85)	12(7.69)
Feeling less attractive	154	90(58.44)	49(31.82)	15(9.74)
Feeling less sexually desirable	151	96(63.58)	39(25.83)	16(10.60)
Feeling less feminine	155	114(73.55)	29(18.71)	12(7.74)
Difficulty in returning to former roles (e.g. job, family, friends)	156	125(80.13)	15(9.62)	16(10.26)
Job discrimination	149	142(95.30)	2(1.34)	5(3.36)
Difficulty in pursuing the career of my choice	146	126(86.30)	8(5.48)	12(8.22)
Not being able to change jobs for fear of losing my health insurance	140	129(92.14)	3(2.14)	8(5.71)
Being concerned about infection	152	116(76.32)	23(15.13)	13(8.55)
Being concerned about crowds	152	122(80.26)	19(12.50)	11(7.24)
Being less able to provide for the financial needs of my family	151	116(76.82)	22(14.57)	13(8.61)
Difficulty in meeting my medical expenses	153	108(70.59)	23(15.03)	22(14.38)
Difficulty in obtaining adequate insurance	152	129(84.87)	12(7.89)	11(7.24)
Not being able to get the information I need about cancer	152	141(92.76)	4(2.63)	7(4.61)
Not being able to get information I need to take care of myself after treatment	153	139(90.85)	6(3.92)	8(5.23)
Being treated as different from others	153	137(89.54)	8(5.23)	8(5.23)
Problems with family/children	151	137(90.73)	8(5.30)	6(3.97)
Problems communicating with my spouse or partner	144	120(83.33)	13(9.03)	11(7.64)
No regular doctor or medical provider	153	139(90.85)	7(4.58)	7(4.58)
No transportation to/from medical visits	154	145(94.16)	5(3.25)	4(2.60)
No money for cost of or co-payment for medical visits	154	125(81.17)	16(10.39)	13(8.44)
No money for cost or co-payment for medicine	154	128(83.12)	13(8.44)	13(8.44)

Table 3 Differences in problems in living by age

Description	OR (95 % CI) (age > 55 *vs.* <= 54 years)	p-value
Trouble concentrating	0.36 (0.13–0.97)	0.0355
Tenderness at surgical site	0.33 (0.12–0.88)	0.0217
Muscle or joint stiffness	0.25 (0.05–0.9)	0.0314
Arm swelling	0.37 (0.13–1.13)	0.0461
Less sexual desire	0.32 (0.11–0.91)	0.0223
Hot flashes	0.09 (0.02–0.34)	0
Sweating	0.17 (0.05–0.51)	3.00E-04
Feeling fearful that my illness will return	0.19 (0.06–0.54)	5.00E-04
Fears about the future	0.27 (0.1–0.72)	0.0047
Having difficulty in making long-term plans	0.30 (0.11–0.83)	0.0167
Feeling emotionally vulnerable	0.26 (0.1–0.72)	0.0043
Feeling helpless	0.28 (0.1–0.8)	0.0107
Feeling angry	0.20 (0.07–0.56)	8.00E-04
Feeling dependent	0.34 (0.12–0.92)	0.0211
Feeling sad	0.16 (0.06–0.45)	1.00E-04
Feeling less attractive	0.32 (0.11–0.88)	0.0203
Difficulty in pursuing the career of my choice	0.22 (0.07–0.72)	0.0057
Not being able to change jobs for fear of losing my health insurance	0.20 (0.04–0.91)	0.0183
Being less able to provide for the financial needs of my family	0.28 (0.1–0.78)	0.0075
Difficulty in meeting my medical expenses	0.23 (0.08–0.62)	0.0013
No regular doctor or medical provider	0.29 (0.08–1.22)	0.0466

Table 4 Differences in problems in living by race

Description	OR (95% CI) (non-whites *vs.* Whites)	P-value
Major problems with my health	2.34(1.12–4.95)	0.0213
Tenderness at surgical site	3.45(1.64–7.4)	5.00E-04
Arm swelling	2.83(1.13–7.2)	0.0153
Guilt feelings	4.4(1.38–15.53)	0.0055
Difficulty in pursuing the career of my choice	3.4(1.17–10.44)	0.0203
Being less able to provide for the financial needs of my family	3.91(1.66–9.42)	8.00E-04
Difficulty in meeting my medical expenses	3.23(1.46–7.22)	0.0021
Difficulty in obtaining adequate insurance	6.48(2.28–20.38)	1.00E-04
Not being able to get the information I need about cancer	11.45(2.23–113.57)	6.00E-04
Problems communicating with my spouse or partner	2.7(1–7.34)	0.0311
No regular doctor or medical provider	6.48(1.74–30.07)	0.0016
No transportation to/from medical visits	4.64(0.94–30.02)	0.0307
No money for cost of or co-payment for medical visits	4.03(1.62–10.37)	0.0015
No money for cost or co-payment for medicine	4.51(1.73–12.31)	9.00E-04

Table 5 Differences in problems in living by marital status

Description	OR (95% CI) (single or divorced *vs.* married/partner)	P-value
Dryness in vagina	2.28(1.14–4.67)	0.0146
Pain during sexual intercourse	4.62(2.05–11.03)	1.00E-04
Less sexual desire	3.49(1.68–7.45)	4.00E-04
Being less able to provide for the financial needs of my family	0.34(0.14–0.79)	0.0068
No money for cost of or co-payment for medical visits	0.27(0.1–0.69)	0.0034
No money for cost or co-payment for medicine	0.27(0.09–0.72)	0.0047

Table 6 Differences in problems in living by household income

Description	OR (95% CI) (income > $50,000 *vs.* < $50,000/year)	P-value
Major problems with my health	0.26(0.12–0.56)	2.00E-04
Being less able to provide for the financial needs of my family	0.38(0.16–0.91)	0.0196
Difficulty in meeting my medical expenses	0.42(0.19–0.95)	0.0306
Difficulty in obtaining adequate insurance	0.35(0.12–0.98)	0.0397
No money for cost of or co-payment for medical visits	0.32(0.13–0.82)	0.0104

low income families), stage of cancer (higher for stages II, III and IV versus ductal in-situ carcinoma) and treatment type (higher for radiation and biologic/targeted therapy *vs.* no-treatment). Coefficients and p-values for the Poisson regression model are presented in Table 7.

Table 7 Coefficients obtained from fitting a Poisson regression model to the total number of problems where the participants responded as having somewhat of a problem/a severe problem

Variable	Coefficient	Standard error	P-value
Intercept	3.346388	0.348489	**< 0.0001**
Age	-0.02508	0.002713	**< 0.0001**
Race - Non-whites	0.205097	0.054332	**0.00016**
Marital status – Married	0.25931	0.053476	**1.24E-06**
Income - < $50,000/year	0.352313	0.058528	**1.75E-09**
Medicare	0.158761	0.238918	0.50637
Medicaid	0.432444	0.254269	0.08899
Private insurance	0.266349	0.244818	0.27662
Other insurance	0.02162	0.254306	0.93225
Stage I	0.057097	0.072323	0.42984
Stage II	0.312948	0.075704	**3.57E-05**
Stage III	0.276776	0.099811	**0.00555**
Stage IV	0.355998	0.109878	**0.0012**
Stage - Do not know	-0.020983	0.084564	0.80403
Time since diagnosis	0.005598	0.003226	0.08265
Radiation	0.235654	0.057858	**4.64E-05**
Chemotherapy	0.002194	0.055726	0.96859
Hormone therapy	-0.031402	0.052014	0.54603
Targeted therapy	-0.275192	0.118568	**0.02029**

4 Discussion

The results of this study indicate that a substantial proportion of breast cancer survivors seen at an academic medical center in the southern United States reported having problems in living such as sleep difficulties, fatigue, loss of strength, aches and pains, and muscle or joint stiffness. Important correlates of having reported symptoms included age, race, marital status, and household income. Madelblatt *et al*. [10] noted that older breast cancer survivors may have a high symptom burden due to comorbidities and aging. However, in the current study, almost all of the symptoms were more likely to be reported by participants who were less than 55 years of age. In a study of problems of living among men and women who were adult cancer survivors, Baker *et al*. [8] found that more problems were reported by younger survivors (ages 18-54 years), women, non-whites, those who were not married, and those with a household income < $20,000 per year. Younger cancer survivors are more likely to still be employed and to have dependent family members [8].

Many cancer survivors identify fatigue as one of the most frequent and distressing cancer-related symptom [11, 12]. In the current study, 56% of the participants reported having fatigue. In a population-based study by Meeske *et al*. [11], 41% of breast cancer survivors who were 2 to 5 years following diagnosis were fatigued. These differences in the frequency of fatigue may be due to differences in study design or patient population. A subset of breast cancer survivors experience moderate to severe symptoms years after cancer treatment has ended [11, 13, 14]. Factors associated with fatigue in breast cancer survivors include pain, sleep problems, physical inactivity, and depression [13–16]. Persistent fatigue following cancer treatment affects survivors' physical well-being and quality of life [11]. Physical activity has been shown to be an effective non-pharmacologic intervention for fatigue in cancer survivors [11, 17–19].

Previous studies have showed that 24% to 84% of breast cancer patients report persistent pain following cancer treatment [2, 20–24]. In the current study, 71% of participants reported aches and pains, which may be partially due to comorbid conditions such as arthritis. About 67% reported muscle or joint stiffness. Report of pain symptoms has been associated with poorer quality of life among breast cancer patients [2]. Results from cross-sectional and longitudinal studies suggest that younger age, more invasive surgery, adjuvant therapy, and psychosocial factors have a role in the development of chronic pain [25, 26]. In the current study, age < 55 years was associated with tenderness at surgical site [OR = 0.33, 95% CI (0.12, 0.88)].

Caregivers should be aware of the increased frequency of problems in living among breast cancer survivors who are non-white or low-income. In the current study, the majority of the

non-white participants were African American. The finding that non-white breast cancer patients were more likely to report certain problems in living highlights the importance of considering the special needs of minority patients in their response to illness [8]. Low-income survivors are particularly vulnerable to experiencing problems in living that are indicators of financial distress including being less able to provide for the financial needs of their family, having difficulty in meeting their medical expenses, having difficulty in obtaining adequate insurance, and not having money for the cost of medical visits.

In the current study, participants who were married or living with a partner were more likely to report sexual problems such as vaginal dryness, pain during sexual intercourse, and having less sexual desire. In prior studies, women who received adjuvant therapy experienced more severe symptoms, including vaginal problems, musculoskeletal pain, and hot flashes [27, 28].

With respect to limitations, misclassification bias is a possibility due to the use of self-reported information. The results of this study may not be generalizable to other populations of breast cancer survivors. However, the sample was diverse by race, socioeconomic factors, and history of breast cancer diagnosis and treatment. A further limitation was the cross-sectional design of the study. In addition, selection bias may have occurred due to the low response rate (16.4%).

Regarding the adequacy of the sample size, we carried out sample size calculations based upon a range of estimates. Assuming an alpha value of 0.05 and power of 0.80, an overall sample size of 136 breast cancer survivors, or 68 survivors per group, would be adequate for a two-tailed test on proportions where P1 = 0.30 and P2 = 0.55. Assuming an alpha value of 0.05 and power of 0.80, an overall sample size of 96 breast cancer survivors, or 48 survivors per group, would be adequate for a two-tailed test on proportions where P1 = 0.30 and P2 = 0.60. Assuming an alpha value of 0.05 and power of 0.80, an overall sample size of 130 breast cancer survivors, or 65 survivors per group, would be adequate for a two-tailed test on proportions where P1 = 0.25 and P2 = 0.50. Assuming an alpha value of 0.05 and power of 0.80, an overall sample size of 94 breast cancer survivors, or 47 survivors per group, would be adequate for a two-tailed test on proportions where P1 = 0.25 and P2 = 0.55. These calculations indicate that the available sample size was adequate to detect clinically significant differences across groups.

Taken overall, the results of this study, when combined with findings from previous reports [2, 10], highlight the need for caregivers to emphasize screening for and discussion of symptoms, including sleep difficulties, fatigue, loss of strength, aches and pains, and muscle or joint stiffness. Of particular concern are younger survivors and those who are African American or low-income. As more attention is given to increasing the quality of life of breast cancer survivors, it is important to identify problems in living, which can help establish which problems should be the focus of possible prevention efforts and supportive care.

Ethics

This study was approved by the Augusta University Institutional Review Board and was compliant with ethical standards.

Conflict of interest

The authors declare they have no conflicts of interest.

Informed consent

The informed consent of research participants was obtained.

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RESEARCH ARTICLE

Day 21 serum Free Light Chain (FLC) levels as a predictor of response to therapy in symptomatic multiple myeloma

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Abstract: **Objective**: To study the predictive value of reduction of involved free light chain level on Day 21 of chemotherapy for achievement of VGPR after 4 cycles of induction chemotherapy. **Methods**: We conducted a prospective observational study in twenty-eight patients of newly diagnosed Multiple Myeloma with iFLC $\geq$ 100 mg/L. Serum FLC assay was done at baseline and on day 21 of therapy. All patients were followed up till the end of induction therapy for response assessment based on the IMWG criteria. Receiver Operator Characteristic (ROC) curve analysis was done to determine the cut off value of per cent reduction in day 21 iFLC for achievement of VGPR or better. **Results:** After the induction chemotherapy, out of 28 patients, 13 patients achieved CR, 8 patients achieved VGPR, 4 patients achieved PR and 2 patients had stable disease ($\geq$ VGPR = 21 patients, $<$ VGPR = 6 patients). One patient expired after 2nd cycle of chemotherapy. The mean per cent reduction in day 21 iFLC level as compared to baseline was 91.5% and 57.1% in patients achieving $\geq$ VGPR and $\geq$ VGPR ($P < 0.0001$), respectively. No other baseline parameter was found to be significantly different between the 2 groups. ROC curve analysis demonstrated a cut off of 84% reduction in iFLC value on day 21 (AUC of 0.937) had a sensitivity of 85.7% and a specificity of 100% in predicting the achievement of VGPR after four cycles of induction chemotherapy. **Conclusion:** Monitoring iFLC levels on Day 21 can be used as an important tool for early identification of responders/non-responders to myeloma therapy. Day 21 serum FLC assay may have a potential role in the real-time assessment of treatment response in newly diagnosed myeloma patients.

Keywords: multiple myeloma, prognosis, serum Free Light Chain assay

1 Introduction

The incidence of Multiple myeloma is increasing with time, in view of the newer investigation modalities and the updated diagnostic criteria. Multiple myeloma is considered to be most treatment sensitive at diagnosis. Overall survival in multiple myeloma has definitely improved in the last 15 years, largely due to the emergence of newer treatment modalities [1]. Almost all patients do relapse post induction and consolidation therapy, hence, markers which detect the relapse of disease are essential during follow up. Tools for detecting the efficacy of therapy are equally important in monitoring the disease response. Though baseline prognostic characters like cytogenetics, ISS scoring and staging to some extent determine the prognosis in plasma cell myeloma, the dynamic parameters like free light chain levels and minimal residual disease are now increasingly used to determine response to treatment and alter therapy if required. With treatment induced reduction in malignant plasma cells, the serum Free Light Chain (sFLC) concentrations tend to decrease rapidly and precipitously. Thus measurement of sFLC levels at short time intervals has been an important guide to the response to treatment, early detection of treatment failure or disease relapse.

There are many studies which have evaluated the importance of involved FLC in the monitoring of patients of multiple myeloma on therapy and early sFLC response indicating efficacy of therapy. The short half-life on free light chains (2-6 hours) as compared to that of M protein (12 days) makes it an important real time marker in determining the early response to therapy in myeloma patients [2]. Attempts have been made to study reduction in involved free light chain post chemotherapy, to monitor response and correlate with the achievement of very good partial response (VGPR) [3]. Studies have shown that normalization of the sFLC ratio and significant reductions in iFLC after initial treatment indicating better response rates. One study conducted by Hansen *et al.* [4] measured the serial levels of M protein and serum free light chain after starting therapy in myeloma patients and concluded that 80% reduction in iFLC at day 21 could

predict the achievement of VGPR post 4 cycles of induction chemotherapy with a sensitivity of 87.5% and a specificity of 100%. In contrast they found that a fall in M-protein could be appreciated only after 130 days of starting treatment. However, Indian data regarding serum free light chain assay as a predictor of response to therapy is lacking. The present study was conducted with an aim to determine the prognostic significance of serum free light chain assay in the assessment of response to therapy in myeloma patients.

2 Aim of the study

To study the predictive value of reduction of involved serum free light chain levels on Day 21 of chemotherapy, from baseline, for achievement of very good partial response (VGPR) after 4 monthly cycles of induction chemotherapy.

3 Materials and methods

This prospective observational study was carried out in the Department of Hematology, Sir Ganga Ram Hospital, over a period of one and a half year. The study was started after obtaining approval from ethics committee. As per the study done by Hansen *et al.* [4], the specificity of fall of iFLC at day 21 to predict achievement of VGPR was 100%. Thus, we have used specificity of 99% for calculating sample size using the two-step formula and minimum of 21 patients were required for our study as per calculation.

3.1 Inclusion & exclusion criteria

Newly diagnosed cases of Multiple Myeloma (based on diagnostic criteria in IMWG guidelines 2014) being started on induction chemotherapy as per standard of care with involved serum FLC $\geq$ 100 mg/L were included in the study. Patients with multiple myeloma with dialysis dependent kidney disease or pre-existing chronic kidney disease (CKD) were excluded from the study. Before enrolling the patient in study the informed consent was obtained. They were explained about the study and also given a detailed patient information sheet. The consent forms were signed after satisfying all queries. A comprehensive clinical history was recorded and complete physical examination was done.

3.2 Investigations

The following investigations were carried out on the patients at baseline(done as per standard of care for Multiple Myeloma): Complete Blood Count (CBC), Differential Leucocyte Count (DLC), Peripheral Smear (PS), Erythrocyte Sedimentation Rate (ESR), Liver function tests (LFT), Kidney function tests (KFT), Bone marrow Aspiration & Biopsy, Lactate dehydrogenase (LDH), along with Serum Protein Electrophoresis (SPEP) and Immunofixation (SIFE), Serum Free Light Chain assay (sFLC), β2 microglobulin, Immunoglobulin levels (the latter 5 investigations collectively done as Comprehensive Myeloma Panel at our institute). FISH analysis for Myeloma was done wherever feasible. Imaging studies including Skeletal survey by X-ray, Magnetic resonance imaging (MRI) or Computerised tomography (CT) scans or whole body Positron emission tomography CT scan (PET-CT) was done as per requirement. One peripheral blood sample on day 21 of chemotherapy was taken for our study to assess the serum free light chain levels and ratio. At the end of induction chemotherapy (4 monthly cycles of triple drug regimen) response to therapy was assessed by repeating the baseline investigations including the comprehensive myeloma panel.

3.3 Technique: Serum free light chain assay

The Freelite Serum free light chain assay was performed using the SPAPLUS analyser by The Binding Site using polyclonal reagents to measure the free light chains [5]. It is an turbidimetric assay composed of two sensitive and specific immunodiagnostic tests to measure kappa (κ) and lambda (λ) free light chains levels. It is based on the principle of turbidimetry, the concentration of a soluble antigen is determined by the addition of the appropriate antibody in a reaction vessel or cuvette. A beam of light, wavelength measuring 600 nm, is passed through the cuvette and, as the antigen-antibody reaction proceeds, light scatter is monitored by measuring the decrease in intensity of the incident beam of light. A series of calibrators of known antigen concentration

are assayed initially to produce a calibration curve of measured light scatter versus antigen concentration and the results are read by the analyser from the calibration curve.

3.4 Treatment

The patients were treated as per protocol [1]. Most patients received Bortezomib-based triple drug regimens. Patients with renal failure were given thalidomide instead of lenalidomide in view of renal safety of thalidomide. One patient received Lenalidomide and Dexamethasone (Two drug regimen) in view of her age and pre-existing comorbidities. All patients received 4-monthly cycles of induction chemotherapy and were assessed for the response of the initial therapy. Eligible patients were taken up for Autologous stem cell transplantation followed by maintenance chemotherapy. Transplant ineligible patients were given maintenance chemotherapy and followed up.

3.5 Follow up

Newly diagnosed cases of multiple myeloma started on induction chemotherapy were followed up until the end of 4 cycles of chemotherapy and assessed for the response to therapy. At the end of 4 monthly cycles of chemotherapy, patients were assessed for the response, based on the serum M-protein level and serum Free Light Chain level, and were divided into 2 groups based on the achievement or not achievement of VGPR (Very Good Partial Response) *i.e* $\geq$ VGPR ($>$ 90% reduction in serum M-protein and if the serum and urine M-protein are unmeasurable, then $>$ 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels) or $<$ VGPR ($<$ 90% reduction in serum M-protein or $<$ 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels).

3.6 Statistical analysis

Data base was created on MS Excel and SPSS software was used for descriptive and inferential analysis. Linear regression analysis was done to assess the correlation between baseline parameters. Comparison between the baseline parameters between the two groups ($\geq$ VGPR and $<$ VGPR) was done using unpaired T-tests. Predictive value of fall in involved free light chain on day 21 was assessed by preparing ROC curves and best cut offs were generated.

4 Results and analysis

A total of 44 patients diagnosed as Multiple Myeloma on the basis of clinical and laboratory parameters as per the new IMWG diagnostic criteria of 2014, along with iFLC $>$ 100 mg/L were enrolled in the study. Out of the 44 patients, 2 patients died within few days of diagnosis, 6 patients were lost to follow up, 2 patients refused to receive chemotherapy and Day 21 blood sample for Free light chain assay could not be obtained in 6 patients. Day 21 sample for free light chain assay was obtained in 28 patients, and all these patients were followed up till the end of induction chemotherapy to assess the response to treatment. One patient died after 2nd cycle of chemotherapy hence, excluded from the analysis. So, the analysis could be done in 27 patients. Baseline investigations were carried out in all 28 patients.

The study flowchart is depicted in Figure 1.

4.1 Results

In our study, 28 patients of MM, with involved FLC $\geq$ 100 mg/L were included and were followed up till the end of chemotherapy to assess for response to treatment. One patient had died after 2nd cycle of chemotherapy hence statistical analysis was done in 27 patients. Along with baseline parameters, serum FLC assay was done on Day 21 of initiation of chemotherapy. After induction chemotherapy, the response assessment as done based on the IMWG criteria.

4.2 Clinical parameters

The median age at diagnosis was 60.3 years and the patients age ranged from 31-81 years, with maximum patients in the 6th and 7th decade with a male: female ratio was 1.33:1(16 males and 14 females). The most common presenting feature in our study was fatigue in 89.2% patients followed by bone pains in 53.5% patients. Hypercalcemia was present in 28.5%, 60.7%

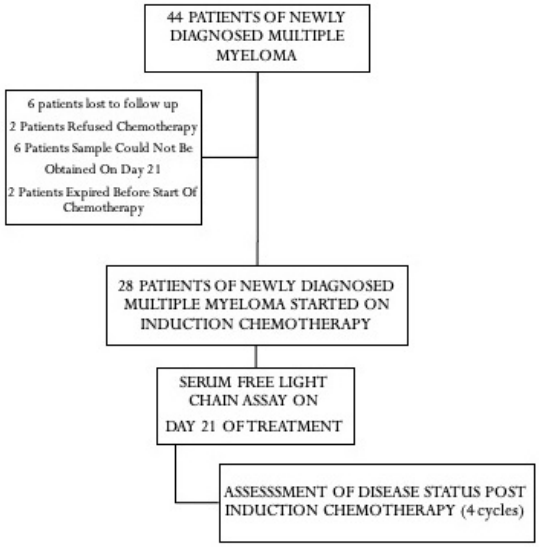

Figure 1 Study flowchart

presented with renal failure, anemia was present in 85.7%, and lytic bone lesions in 71.5% patients. We had an increased proportion of patients with renal failure.

4.3 Laboratory parameters

Patient characteristics and the median laboratory values are illustrated in Table 1.

Table 1 General characteristics of the study population (N = 28)

Variable	Value
Age	**Mean(Range)**
	60.3 (31-81)
Sex	**N(%)**
Male	16 (57%)
Female	12 (43%)
M-protein	**N(%)**
IgG	12 (43%)
IgA	8 (28%)
Light chain only	4 (14%)
Involved free light chain	**N(%)**
Kappa	15 (54%)
Lambda	13 (46%)
Treatment regimen	**N(%)**
BRD	14 (50%)
BTD	12 (43%)
RD	1 (3.5%)
CyBorD	1 (3.5%)
Pretreatment variables	**Median(Range)**
M protein (g/L)	3.27 (0.53-5.99)
iFlc (mg/L)	1948 (101.8-36766)
FLC ratio	87.38 (6.16-593.2)
Laboratory parameters	**Median(Range)**
Hb (g/dL)	7.8 (5.2-13.2)
Creatinine (mg/dL)	1.98 (0.46-15.98)
e-GFR (ml/min)	31.4(2.5-112.8)
Calcium (mg/dL)	9.75 (8.4-16)
ESR (mm 1st hr)	89 (2-160)
ISS	**N(%)**
I	1 (4.5%)
II	4 (18%)
III	17 (77.5%)

Amongst the baseline parameters, we found significant correlation between the serum creatinine and involved free light chain levels and ratio which indicate that renal involvement is associated with increased iFLC levels and FLC ratio, as the free light chain excretion is impaired in renal failure. There was also significant correlation between the β 2-microglobulin and involved FLC and involved/uninvolved FLC ratio, *i.e.* in patients with higher levels of the β 2-microglobulin, the iFLC and ratio were higher. However, we did not find any significant correlation between other baseline parameters.

4.4 Serum FLC assay on Day 21

We found that involved FLC value on Day 21 was decreased in all patients with a mean reduction of 84.34% (Range: 29.83-99.82%) and there was $\geq$ 80% decrease in iFLC in 21 patients and 7 patients had $<$ 80% decrease in iFLC.

4.5 Assessment of response to therapy

We assessed the response to treatment after 4 cycles of initial chemotherapy as per IMWG response criteria and out of 27 patients, 13 patients had achieved CR, 8 patients achieved VGPR, 4 patients had PR and 2 patients had Stable disease. 21 out of 27 patients (77.8%) had achieved $\geq$ VGPR and 6 patients (22.2%) had achieved $<$ VGPR.

We found a significant difference in percentage decrease in involved free light chain on Day 21 in patients who achieved $\geq$ VGPR (91.5% $\pm$ 12.4) and those patients who did not achieve VGPR (57.1% $\pm$ 21.3) with a P value of $<$0.0001. (Figure 2)

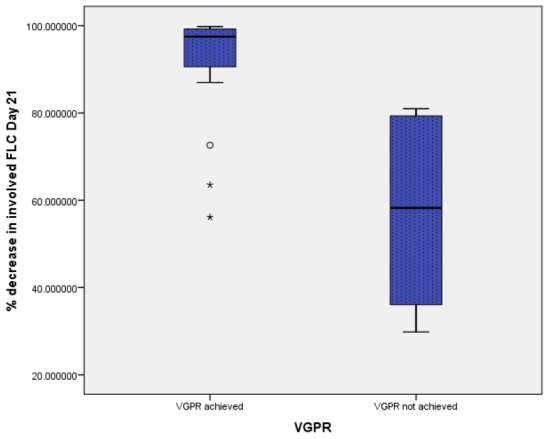

Figure 2 Boxplots for % decrease in involved FLC on day 21 between VGPR achieved and not achieved

In patients who achieved $\geq$ VGPR, the mean percentage reduction in iFLC on day 21 was 91.5% which was comparable to the study by Hansen *et al.* in which the mean percentage reduction in iFLC on day 21 was 92.3%. We found no significant difference between the hematological and biochemical parameters in patients who achieved $\geq$ VGPR and $<$ VGPR.

4.6 Correlation between reduction of iFLC on Day 21 and achievement of $\geq$ VGPR

The main objective of our study was to assess the sensitivity and specificity of % reduction in involved free light chain level on Day 21 to assess the achievement of $\geq$ VGPR. We analysed the % reduction in involved free light chain level on Day 21 in patients who achieved $\geq$ VGPR and $<$ VGPR and ROC curves were generated (Figure 3) and a reduction of 83.99% (84%) was found to be the best cut off to predict the achievement of VGPR with a sensitivity of 85.7% and a specificity of 100% with AUC (area under the curve Table 2) of 0.93.

Table 2 Area under the curve (Variable(s): DECPERINVFLC21)

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.937	0.046	0.001	0.846	1.000

Notes: a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5

There was no correlation between baseline parameters and percentage reduction in FLC on day 21 using linear regression analysis.

We analyzed the sensitivity and specificity of reduction in iFLC on Day 21 in predicting renal recovery. We had 13 patients with serum creatinine of $\geq$ 2 mg/dL who were assessed for renal recovery. We found that 84% reduction in iFLC value was associated with renal recovery with a sensitivity and specificity of 77.7% and 75% respectively.

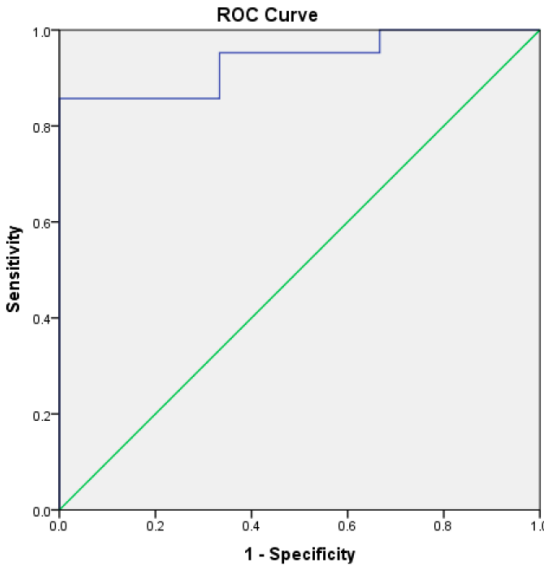

Figure 3 ROC analysis

5 Discussion

As with other haematological malignancies, in Multiple Myeloma there are a plethora of markers at diagnosis including adverse cytogenetics which predict survival [1]. However the true measure of the patient's survival and prognosis is the response of the disease to the available treatment. A patient with good risk baseline features at times do not respond well to treatment whereas the patients with predicted poor outcome achieve remission with aggressive chemotherapy. Therefore more and more the functional and real time parameters of disease are being used to predict the course of disease.

Serum Free Light Chains have shorter half-life and with the development of robust assays, involved free light chains in patients of multiple myeloma can be measured rapidly and can predict much earlier the response to chemotherapy [2]. Studies have shown that the patients who achieved VGPR have better event free and progression free survival. The rapid and greater percentage reduction in involved serum free light chain has been found to be associated with attainment of VGPR and hence can help in predicting the prognosis and course of disease.

A number of studies have looked into the prognostic effect of involved free light chain (iFLC) and the serum free light chain ratio at baseline as a marker of survival [6, 7]. In addition, a few studies have assessed the early reduction of free light chain levels to predict the response to therapy as compared to the reduction in M protein levels.

Mead *et al.* [8] in their study in 17 patients of MM had noted that the extent of change in the FLC concentrations was seen to be greater than that of the total intact immunoglobulin in all patients, the range of FLC reduction being 2.11678-fold (mean 219-fold) as compared to the range of total, intact immunoglobulin reduction was 1.588-fold (mean 14.6-fold). Dejoie *et al.* [9] in 2016 have evaluated 113 patients of MM and found that elevated iFLC or an abnormal κ / λ sFLC ratio after 3 treatment cycles associated with poorer PFS ($p = 0.006$ and $p < 0.0001$, respectively) along with poor overall survival($P = 0.022$).

However, there are a few studies with contrasting outcomes. Dispenzieri *et al.* [10] in 2008 analyzed the value of serum free light chain levels in 399 patients of multiple myeloma and had assessed the reduction of both serum FLC and M protein levels two months following induction therapy and not find serum FLC monitoring to have an added advantage over measurement of M protein. They have also concluded that baseline FLC could not predict the survival (OS and PFS) in contrast to other studies. Mori *et al.* [11] studied 73 newly diagnosed multiple myeloma patients receiving induction therapy and have stated that addition of FLC to M-protein further informs the characterization of residual disease status post-induction therapy as a biomarker, but M protein according to them was a better indicator of disease response. Van Rhee *et al.* [12] in their study, measured the SFLC levels at baseline, within 7 days of first cycle, before second induction cycle and before first transplantation, and have concluded that high baseline levels of FLC ($\geq$ 750 mg/L) along with steeper reduction after therapy indicated more aggressive disease and was associated with inferior survival. This higher reduction indicating inferior survival is in

contrast to the other studies which mention that more reduction in involved FLC indicates better survival.

Hansen *et al.* [4], in their study in 36 patients with symptomatic multiple myeloma, had measured values of iFLC and M-protein at the baseline, every day for 5 week days from the start of treatment, and after 2, 3 and 6 weeks. Ten patients with iFLC >75 mg/L achieved a reduction of 80% or more at day 21 after start of treatment and nine of these obtained ≥ VGPR. They had found that 80% reduction in iFLC at day 21 could predict the achievement of VGPR post 4 cycles of chemotherapy with a sensitivity of 87.5% and a specificity of 100%, where as a fall in M protein could be appreciated only after 130 days of starting treatment. hence Day 21 can be used as a reasonable time point to assess changes in iFLC to predict the goal of achieving at least VGPR post chemotherapy.

In our study, 28 patients of MM, we found a significant difference in percentage decrease in involved free light chain on Day 21 in patients who achieved ≥ VGPR (91.5% ± 12.4) and those patients who did not achieve VGPR(57.1% ± 21.3) with a P value of < 0.0001. In patients who achieved ≥ VGPR, the mean reduction in iFLC on day 21 was 91.5% which was comparable to the study by Hansen *et al.* in which the mean reduction in iFLC on day 21 was 92.3%. We found no significant difference between the hematological and biochemical parameters in patients who achieved ≥ VGPR and < VGPR. The baseline levels of iFLC were very diverse among our patients ranging from 101.8-36,776 mg/L, thus the per cent reductions in very high baseline values have the possibility of declining faster and steeper than lower values as has been discussed by Dispenzieri *et al.* [10].

The main objective of our study was to assess the sensitivity and specificity of per cent reduction in involved free light chain level on Day 21 to assess the achievement of ≥ VGPR. We analysed the percentage reduction in involved free light chain level on Day 21 in patients who achieved ≥ VGPR and < VGPR and ROC curves were generated and a reduction of 83.99% (84%) was found to be the best cut off to predict the achievement of VGPR with a sensitivity of 85.7% and a specificity of 100%, and AUC of 0.937. Hansen *et al.* [4] have found a cut off of 80% reduction in iFLC at day 21 as a predictor of VGPR to provide a sensitivity of 87.5% and a specificity of 100%. The mild difference in the cut off in both the studies (84% *vs* 80%) could be due to the higher disease burden in our population requiring higher reduction of FLC on day 21 to predict the achievement of VGPR. Hansen *et al.* [4] had also measured the M protein levels on Day 21 and had not found significant reduction in M protein levels in view of the long half-life of M protein and a decrease of > 90% could be obtained after 130 days of start of therapy. Hence measurement of M-protein levels on Day 21 was not done in our study. (see Table 3)

Table 3 Comparison of our study with the study by Hansen *et al.* [4]

Study	% reduction in iFLC to predict achievement of VGPR	Sensitivity (%)	Specificity (%)
Our study	84	85.7	100
Hansen *et al.* [3]	80	87.5	100

There are a few studies showing early decrease in involved free light chain was associated with improved renal outcome in MM patients. Hutchison *et al.* [13] in their study on 39 patients with biopsy proven myeloma kidney, had found a linear relationship between FLC reduction and renal recovery, with a 60% reduction in FLC by day 21 being associated with renal recovery for 80% of the population. A retrospective analysis of 279 patients by Sugihara *et al.* [14] have found that reduction of iFLC 95% at day 21 (P = 0.015) and urinary albumin ≦ 25% (P = 0.007) was significant for any renal response in patients with myeloma kidney. In our study, we found that 84% reduction in iFLC value was associated with renal recovery with a sensitivity and specificity of 77.7% and 75% respectively. Early reduction of iFLC in predicting renal recovery was established in the above studies, however, due to small sample size in our study, we could not establish a definite correlation between early decrease in iFLC and renal recovery. A study on a larger number of Indian patients with renal involvement may be required to shed light in the aspect.

We also analysed the correlation between baseline parameters and percentage reduction in FLC on day 21 using linear regression but we did not find any significant correlation between the two. There was also significant correlation between the β2-microglobulin and involved FLC and involved/uninvolved FLC ratio at baseline, *i.e.* in patients with higher levels of the β2-microglobulin, the iFLC and ratio were higher, indicating higher burden of disease as β2-microglobulin is an established independent prognostic marker in MM.

In our study, though the number of patients were less due to limitations of time, we could clearly demonstrate the importance of adding serum free light chain assay on day 21 of induction

chemotherapy as a surrogate marker of response to therapy by measuring the per cent reduction of iFLC as compared to baseline.

There are a few limitations in our study. Firstly, the number of patients in the group that did not achieve VGPR (6 patients) is very less compared to the patients who have achieved VGPR or more (21 patients). Secondly, all the patients could not be followed up to assess the overall survival (OS) and progression free survival (PFS) as the duration of our study was limited. However, we do plan to extend the study further. So, Serum free light chain assay being a simple and effective test to assess the burden of disease, evaluation of Day 21 serum free light chain assay could have a potential role as an early predictor of response to therapy.

6 Conclusion

Serum Free Light Chain assay on Day 21 of starting treatment can be done as a surrogate marker to predict the response to therapy in Multiple Myeloma early in the course of the treatment and $> 84\%$ reduction of iFLC is strongly associated with achievement of VGPR or better. This parameter could also be utilized in intensification or change of therapy if required. However, it is needed to investigate further to assess the reduction of iFLC on Day 21 for prediction of overall response.

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REVIEW

Financial assistance programs for cancer patients

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Abstract: Background: The high costs of oncology care can lead to financial stress and have deleterious effects on the well-being of patients and their families. However, only a handful of financial assistance programs for cancer patients have been implemented and evaluated to date. Recent findings: Key features of reported programs include instrumental support through financial navigation or education for patients, and financial or charitable support for healthcare costs. Only one of the programs successfully reduced actual out-of-pocket costs for patients, though others were associated with psychosocial benefits or increased knowledge of financial resources. Four of the 5 programs evaluated to date were pilot studies with small sample sizes, and most lack control groups for comparison. Conclusions: Additional studies are needed that include larger sample sizes and with comparison groups of cancer patients in order to determine whether the counseling and navigator programs are effective in addressing financial distress in this patient population. Of particular interest are programs designed for low-income patients and those who lack health care insurance. Financial assistance programs that implement solutions at different levels of the healthcare system (individual patients, providers, healthcare institutions) are more likely to be effective. Multi-level interventions are needed that address the systems in which patients access care, the actual costs of services and drugs, and the individual needs of patients in order to reduce financial hardship for cancer patients.

Keywords: cancer, costs, financial distress, financial toxicity

1 Background

In the past two decades, a burgeoning literature has emerged documenting the problem of financial distress among cancer patients [1–4]. The high costs of oncology care can lead to financial stress and have deleterious effects on the well-being of patients and their families [5]. Financial hardship in cancer patients has been shown to be associated with decreased treatment adherence, poorer quality of life, and worse survival [6]. Cancer patients may struggle to pay out-of-pocket expenses due to the high expenses incurred, the medical debt, or loss of work [2, 7]. Women, younger patients, racial and ethnic minorities, low-income patients, and those without health insurance have an increased risk of financial distress [8, 9]. A framework of financial hardships developed by Altice *et al*. [10] considers three areas of hardship: material conditions (actual costs to the patient, including direct and indirect costs), psychological response (stress caused by the direct/indirect costs of care), and coping behaviors (behavioral responses like skipping medications or delaying care). This framework has been widely adopted within oncology.

While the high prevalence and importance of financial distress among cancer patients is clear from published studies, only a handful of financial assistance programs for cancer patients have been implemented, evaluated, and reported to date.

2 Methods

The present review is based upon bibliographic searches in PubMed and CINAHL and relevant search terms. Articles published in English through December 1, 2020 were identified using the following MeSH search terms and Boolean algebra commands: (financial distress OR financial toxicity) AND cancer. The searches were not limited to words appearing in the title of an article nor to studies in a particular country or geographic region of the world. The references of review

articles were also reviewed. Information obtained from bibliographic searches (title and topic of article, information in abstract, study design, and keywords) was used to determine whether to retain each article identified in this way. Only intervention studies written in English that examined financial distress/toxicity in cancer patients were eligible for inclusion. A total of 5 articles were identified in the bibliographic searches that met the study criteria

3 Results

Shankaran *et al*. [6] developed a financial navigation program in collaboration with Consumer Education and Training Services (CENTS) and the Patient Advocate Foundation (PAF), to improve patient knowledge about treatment costs, provide financial counseling, and to help manage out-of-pocket expenses (Table 1). The PAF is a national organization that assists patients with a range of issues, including access to health insurance coverage, drug copayment assistance, coverage denials, transportation and meals, debt relief, and disability applications [6]. In a pilot study, 34 cancer patients with nonmetastatic solid tumors received an in-person or online financial education course followed by monthly contact with a financial counselor and a PAF case manager for 6 months. Caregivers were encouraged to participate in all aspects of the program. The educational content focused on money management, finding copayment assistance for high-cost drugs, and understanding and navigating health insurance plans. The financial counselors assisted with budgeting, retirement planning, and questions about medical bills. A counselor assigned to each patient arranged an initial meeting to review the patient's expenses, income, and assets, and to provide a prospective budget or financial strategy. The case managers assisted with applications for insurance coverage, cost of living issues (for example, transportation), and disability applications. High financial burden and anxiety about costs were reported at baseline by 37% and 47% of patients, respectively [6]. Although self-reported financial burden did not change over time, anxiety about costs decreased in 33% of patients.

Table 1 Studies of financial assistance programs for cancer patients

Author (location)	Design	Outcomes	Sample	Results
Shankaran et al. [6] (Seattle, WA)	Non-randomized pilot study of an in-person or online financial education course followed by monthly contact with a financial counselor and a case manager for 6 months.	Self-reported financial burden and anxiety about costs	34 cancer patients with nonmetastatic solid tumors	High financial burden and anxiety about costs were reported at baseline by 37% and 47% of patients, respectively [6].
Watabayashi et al. [11] (Seattle, WA)	Non-randomized pilot study	Baseline and 6-month follow-up reports of patient financial hardship using the Comprehensive Score for Financial ToxicityPatient-Reported Outcomes and caregiver work and financial strain using the Caregiver Strain Index measure	32 cancer patients and 18 primary caregivers for those patients	Financial burden and caregiver stress did not change significantly during the pilot despite the fact that participants received a mean of $772 per household (with an additional $647 for some families with non-medical expenses).
Sadigh et al. [14] (Atlanta, GA)	Non-randomized pilot study	This study used the COST tool as a measure of financial distress at study entry and 3, 6, and 9, and 12-months and tracked the number of issues patients discussed regarding debt, disability, employment, insurance, medical decision-making and psychosocial support.	12 brain cancer patients	At 3 months, five patients who completed a follow-up COST tool measurement showed no significant difference in scores from baseline; two of the total 12 patients completed the COST tool at 12 months, with only one-point difference from initial COST assessment. Patients discussed 12 total issues with counselors, of which 93% were resolved within 6 months, with a total of $15,110 debt relief assistance provided.
Kircher et al. [16] (Chicago, IL)	Two-arm randomized controlled trial	Self-reported financial distress, health-related quality of life, and acceptability	95 patients with advanced solid cancers receiving intravenous chemotherapy	No significant changes in financial distress were found between arms. Seventy-six percent of patients reported having no difficulty understanding the information, suggesting high clarity.
Yezefski et al. [15]. (four hospitals in the United States)	Non-randomized evaluation study	Data on financial assistance and hospital revenue. Outcomes for patients included: annual counts of the number of patients receiving navigation, the amount of assistance, and the types of assistance (free medication, new insurance enrollment and benefit maximization, premium/co-pay assistance, transportation, medical equipment).	Financial navigators at 4 hospitals	Trained financial navigators saved patients $39 million in financial assistance, an average of $3.5 million per observation year [15]. Patients saved an average of $33,265 annually on medication most often through connecting patients to foundations or pharmaceutical assistance programs, $12,256 through assistance with enrollment in insurance plans, $35,294 with premium assistance paid by the hospitals, $3076 through referrals to co-pay assistance programs.

A follow-up to this pilot study [11] expanded to caregivers included a financial education video, monthly contact with a CENTS counselor and PAF case manager for 6 months, and referral to the non-profit charitable assistance program, Family Reach, for help with unpaid cost-of-living

expenses (*e.g.*, transportation, housing). Outcomes were measured as baseline and follow-up reports of patient financial hardship using the Comprehensive Score for Financial ToxicityPatient-Reported Outcomes [12] and caregiver work and financial strain using the Caregiver Strain Index (CSI) measure [13]. Among 32 patients and 18 primary caregivers for those patients, financial burden and caregiver stress did not change significantly during the pilot despite the fact that participants received mean of $772 per household (with an additional $647 for some families with non-medical expenses) which may not be enough to overcome stress due to the comparative thousands of dollars for the costs of cancer care. The authors note that the type of assistance needed varied by the participant's income level, with lower-income individuals most often needing help to meet basic cost-of-living expenses such as transportation and housing (66% of participants with incomes of less than $50,000 received cost-of-living assistance), and higher-income participants needing help with issues of employment, medical cost coverage, and insurance navigation.

The PAF was also used in a single-arm pilot oncology navigation program for 12 brain cancer patients by Sadigh, *et al.* [14]. This study used the COST tool [12], as a measure of financial distress at study entry and 3, 6, and 9, and 12-month following and tracked the number of issues patients discussed regarding debt, disability, employment, insurance, medical decision-making and psychosocial support. At 3 months, five patients who completed a follow-up COST tool measurement showed no significant difference in scores from baseline; two of the total 12 patients completed the COST tool at 12 months, with only one-point difference from initial COST assessment. Patients discussed 12 total issues with PAF counselors, of which 93% were resolved within 6 months, with a total of $15,110 debt relief assistance provided.

In a pilot study conducted by Kircher *et al.* [16] 95 patients with advanced solid cancers receiving intravenous chemotherapy were randomly assigned to a financial counseling intervention or to standard care. The financial counseling intervention included a telephone and in-person consultation with a financial counselor that included health insurance education and an estimate of out-of-pocket expenses and total billed charges for one cycle of chemotherapy, including cost of drug, administration, and supportive intravenous medications. Seventy-six percent of patients reported having no difficulty understanding the information, suggesting high clarity. The results suggested that the telephone intervention was more feasible than the in-person consultation with a financial counselor. The authors noted that inclusion of responsible household members is important as patients may not handle their insurance or financial issues.

While most studies have focused on providing education or assistance to patients, one study focused on training staff on how to administer financial assistance. Yezefski *et al.* [15] trained financial navigators at 4 hospitals through the NaVectis Group, an organization that provides training to healthcare staff to increase patient access to care and assist with out-of-pocket expenses. Key components of the program included providing education and training to healthcare staff on how to improve patient access to financial assistance, implementing systematic processes for identifying patients in need, obtaining or improving insurance coverage for patients, and using tracking software to quantify benefits. To evaluate the impact of the program, data regarding financial assistance and hospital revenue were collected after instituting these programs. Outcomes for patients qualifying for assistance included: annual counts of the number of patients receiving navigation, the amount of assistance, and the types of assistance (free medication, new insurance enrollment and benefit maximization, premium/co-pay assistance, transportation, medical equipment). Outcomes were assessed from 2012-2016, with each hospital participating in the program for 1 up to 5 years (totaling 11 years of observation time), and offering different sets of services. Across all hospitals, an average of 32% (n = 3,572) of 11,186 new patients with cancer seen between 2012 and 2016 qualified for assistance. Trained financial navigators saved patients $39 million in financial assistance, an average of $3.5 million per observation year [15]. Patients saved an average of $33,265 annually on medication most often through connecting patients to foundations or pharmaceutical assistance programs, $12,256 through assistance with enrollment in insurance plans, $35,294 with premium assistance paid by the hospitals, $3076 through referrals to co-pay assistance programs. Referrals to community assistance programs helped patients with non-medical direct costs such as transportation, averaging $900 per patient. Hospitals benefited by avoiding write-offs and saving on charity care by an average of $2.1 million per year [15]. While the program was associated with cost-savings for patients and hospitals, the authors note that they did not have similar hospitals that did not use trained financial navigators to which to compare results.

4 Discussion

Key features of the reported programs included instrumental support through financial navigation or education for patients, and some provided financial or charitable support for healthcare costs.

One program successfully reduced actual out-of-pocket costs for patients [15]. Although evaluative results from financial counselor and financial navigator interventions are promising [6, 15, 16], the number of programs is few. Four of the 5 programs evaluated to date were pilot studies with small sample sizes, and most lack control groups for comparison. Additional studies are needed that include larger sample sizes and with comparison groups of cancer patients in order to determine whether the counseling and navigator programs are effective in addressing financial distress in this patient population. Of particular interest are programs designed for low-income patients and those who lack health care insurance.

As institutions consider developing new interventions, educational components should focus on: educating patients about the basics of health insurance and costs they may face during treatment, as well as patient financial assistance programs; making patients aware of potential costs by providing estimates of cancer care costs; and offering education and assistance to patients about insurance benefits and other financial aid that may be available to them [17]. Nonetheless, the lack of cost-savings for education interventions suggest that cost transparency or education on costs will not be enough to sufficiently reduce patient cost burden.

While education-based interventions may help patients to manage anxiety around financial burden, increasing awareness of costs does not decrease costs, and does not solve the underlying issue that costs are too high. Thus, in addition to educational programs, the incentive systems that keep costs high need to be changed. The results of the existing interventions suggest that lowering the costs of care, offering instrumental support through navigation services that connect patients directly to assistance, or having hospitals cover the cost of care when needed are more successful strategies for reducing costs than awareness.

Other forms of instrumental support may include connecting patients to other types of assistance programs. Prescription assistance programs are offered by pharmaceutical manufacturers and charitable foundations to provide medications at reduced or no cost to medically indigent patients [18]. However, identifying strategies to assist with medications may be valuable but may not reduce overall burden or anxiety about cancer-related financial hardship. Nevertheless, prescription assistance programs provide a valuable safety net to help ensure that uninsured cancer patients receive needed prescription medications [18]. Manufacturer-sponsored copay assistance programs generally provide support for a specific drug but unfortunately Medicare beneficiaries are not typically eligible for these programs [19]. However, both patients with private insurance and Medicare beneficiaries can receive support from charitable co-payment assistance programs [19]. There is however little information on the reach of these programs, including the percentage of those helped among applicants, the effect on adherence and outcome and other elements that would be valuable to better understand their reach and limitations.

Financial assistance programs that implement solutions at different levels of the healthcare system (individual patients, providers, healthcare institutions) are more likely to be effective [5]. For example, at the hospital level, strong measures that hospitals can take to address financial toxicity include cost transparency and provision of financial counselors [5]. Interventions addressing laws governing drug pricing, provider reimbursement, and addressing the role of pharmacy benefit management on insurance premiums [20] can influence cost-savings for both care and medications. We need multi-level interventions that address the systems in which patients access care, the actual costs of services and drugs, and the individual needs of patients in order to truly reduce financial hardship for cancer patients.

Conflict of interest

The authors have no conflicts of interest to disclose.

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RESEARCH ARTICLE

Cigarette smoking after surviving breast cancer: A pilot study

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Abstract: **Background**: Quitting smoking improves cancer survival and improves symptoms of cancer and its treatment. Cancer diagnosis presents a powerful motivation for leading a healthier lifestyle and embracing behavioral changes, such as quitting smoking. Many smokers quit after a cancer diagnosis, but some survivors continue to smoke. This study examined the characteristics associated with being a former rather than a current smoker among women treated for breast cancer. **Methods**: In this pilot, cross-sectional study, data were collected via postal surveys in women who had a history of smoking and breast cancer (N = 69). Descriptive and logistic regression analyses were conducted to identify factors associated with smoking status. **Results**: Of this sample, 13 were current smokers and 56 were former smokers. Age, race, education, and employment status were not associated with smoking status. Women with a higher income were significantly more likely to have successfully quit smoking (former smoking OR = 5.94, $p < 0.05$). Most women were light smokers and reported intentions to quit. **Conclusion**: The study attests to the addictive nature of smoking and the difficulty in achieving successful quitting even after breast cancer diagnosis. Results highlighted the role of low income as a barrier in smoking cessation. A follow up study is warranted to uncover potential barriers to smoking cessation in order to individualize tobacco treatment to meet the needs of motivated light smoking cancer patients. Intensive innovative tobacco treatment approaches are warranted, to reach successful cessation particularly among cancer patients with lower income.

Keywords: cigarette, former smoker, financial stress, income, addiction, breast cancer

1 Introduction

With increases in cancer survivors due to advances in cancer treatment and health care, quitting smoking among cancer survivors is necessary to improve long-term outcomes among both tobacco-related and other cancers. Although cigarette smoking is not an established, but a suggested, cause of breast cancer [1,2], continued smoking has detrimental effects on cancer treatment and survival, and symptoms associated with cancer and its therapy. For example, tobacco smoking after breast cancer diagnosis and treatment has been linked to increased overall and breast cancer-related mortality [3–5]. Although the health benefits of quitting are well-established, and cancer patients are strongly advised to quit, smoking sometimes persists even after a cancer diagnosis. Psychological factors such as anxiety, stress, depression, and fear of cancer recurrence have been shown to hinder cessation efforts in cancer patients [6].

Smoking is established and maintained by the intake of the dependence-producing drug, nicotine. Indeed, two thirds (68%) of adult smokers in the United States want to quit and half of them report a past-year quit attempt (stop smoking for > 24 hours) [7]. Unfortunately, the majority of quit attempts fail [8] largely because of nicotine dependence [9]. Some smokers may need up to 30 quit attempts before attaining successfully smoking cessation [8]. In patients with cancer, nicotine withdrawal symptoms [10], *e.g.* irritability, anger, anxiety, and insomnia, may exacerbate cancer associated physical, psychological, and financial stresses. The goal of this study was to examine the characteristics associated with being a former rather than a current smoker among women with a history of smoking and breast cancer.

2 Methods

2.1 Study sample

Data are from the Cardiovascular Disease outcomes among Breast Cancer Survivors (CVD-BCS), a cross-sectional study among a convenience sample of breast cancer survivors. Data

were collected by postal survey questionnaires. Out of the 1000 eligible women invited to participate in the CVDBCS study, 165 of them responded (response rate 16.4%). Inclusion criteria included patients treated for breast cancer at Augusta University Health or the Georgia Cancer Center, they completed primary therapy for the disease, and they were over 18 years of age. All of the patients lived in the Central Savannah Regional Area; and had complete responses on questions pertaining to cigarette smoking status. Of 164 breast cancer survivors who responded to the survey, 156 women had complete data on cigarette smoking. The majority (n = 87, 55.8%) were never smokers. This study focuses on former and current smokers (N = 69).

2.2 Measures

2.2.1 Cigarette smoking status

Women who have ever smoked a cigarette and currently smoke every day or some days were categorized as *current smokers*. Those who have ever smoked and responded *not at all* to the smoke now question were classified as *former smokers*. Furthermore, heaviness of smoking was assessed by number of cigarettes smoked per day (CPD). Information were also collected on past 12 months quit attempts and future intentions to quit.

2.2.2 Participant characteristics

Demographic and other characteristics included in this study were age, race (White, and non-White), education (< high school or high school graduate, some college or college or advanced degree), annual household income (<$50,000 vs $50,000 +) , number of people in household (1 vs 2 or more), employment status (employed vs not employed: retired, on disability, homemaker and temporary unemployed), marital status (married/with partner vs not married: single or widowed or separated/divorced), perceived general health (excellent/very good/good vs fair/ poor).

2.3 Statistical analysis

Descriptive and logistic regression analyses were conducted using R. We present point estimates in the form of percentages and odds rations as well as their 95% Confidence Intervals (CI). Significance level was set at $\alpha = 0.05$. Overall and by participant characteristics, we computed the point estimates and 95% CI of the proportions of current and former smoking. Bivariate models of logistic regression were fitted where smoking status was the dependent variable (former smoker vs current smokers). Independent variables included characteristics such as age, race, education, and household income.

3 Results

Participant characteristics are presented in Table 1. Of breast cancer survivors with a history of tobacco use, 47 (68.12%) were aged 64+ years, 47 (73.44%) were non-white, 43 (66.15%) had at least some college education, and 21 (44.68%) had an annual income of $50,000 or higher. Of this sample, 13 were current smokers and 56 were former smokers. No variation in rates of smoking by age, race, education, employment, and household size were observed. Women with income of $50,000 or higher were significantly more likely to be former smokers than current smokers (former smokers 90.48% vs current smokers 9.52%; OR = 5.94, p = 0.04) as shown in Table 1.

Of the 13 current smokers, 10 women were light smokers (1-10 CPD). Only two (2/13) reported moderate – heavy smoking (11+ CPD). Many (7/13) of the current smokers reported at least one quit attempt in the past 12 months. Almost all (11/13) of the women reported intending to quit smoking in the future (one in the next 30 days, six in the next 6 months, one in the next year, and two later than 1 year).

4 Discussion

Continued smoking in breast cancer survivors, seen at an academic medical center in the southern United States, was observed in 23% of women with a history of cigarette smoking in this pilot study. Demographic factors, such as age, race, and education were not associated with smoking status. However, compared to former smoking, current smoking was positively associated with earning less than $50,000 per year. We posit that this relationship between lower annual household income and continued smoking after breast cancer treatment, could

Table 1 Characteristics of study sample, overall and by smoking status (N = 69)

Characteristics	Overall	Current Smokers (n = 13)	Former Smokers (n = 56)			
	n (%)	n(%)	n(%)	OR	95% CI	*p*
Age						
< 64	22 (31.88)	5 (22.73)	17 (77.27)	Ref		
64+	47 (68.12)	8 (17.02)	39 (82.98)	1.43	0.39 – 4.96	0.57
Race						
White	17 (26.56)	11 (23.4)	36 (76.6)	Ref		
Non-White	47 (73.44)	2 (11.76)	15 (88.24)	2.29	0.53 – 15.97	0.32
Education						
≤ High School	22 (33.85)	7 (31.82)	15 (68.18)	Ref		
Some College +	43 (66.15)	6 (13.95)	37 (86.05)	2.88	0.38 – 10.37	0.10
Household income						
< $50,000	26 (55.32)	10 (38.46)	16 (61.54)	Ref		
$50,000 +	21 (44.68)	2 (9.52)	19 (90.48)	5.94*	1.32 – 42.46	0.04*
Number of people in household						
1	26 (38.24)	3 (11.54)	23 (88.46)	Ref		
2+	42 (61.76)	10 (23.81)	32 (76.19)	0.42	0.09 – 1.54	0.22
Employment status						
Not employed	58 (85.29)	9 (15.52)	49 (84.48)	Ref		
Employed	10 (14.71)	4 (40)	6 (60.00)	3.63	0.80 – 15.54	0.08
Marital status						
Married/partner	32 (47.06)	6 (18.75)	26 (81.25)	Ref		
Not married	36 (52.94)	7 (19.44)	29 (80.56)	0.96	0.28 – 3.24	0.94
Perceived general health						
Excellent-Good	55 (80.88)	9 (16.36)	46 (83.64)	Ref		
Fair-Poor	13 (19.12)	4 (30.77)	9 (69.23)	0.44	0.11 – 1.90	0.24

Notes: * $p < 0.05$

be explained by stress, anxiety, and depression – known predictors of relapse and continued smoking in the general population and in cancer patients [6, 11] – commonly induced by financial distress and the adverse impact of a cancer diagnosis on the financial well-being of patients [12]. In the study, the majority of current smokers wanted to quit and attempted to quit, yet relapsed to smoking. Failed attempts usually result from lack of support and underutilization of effective methods, combined counseling and pharmacotherapy [7]. The cost and unaffordability of approved cessation treatments, such as nicotine replacement therapy, Bupropion-SR, and Varenicline, may pose a barrier to use [13], especially among patients with lower income and cancer-related medical expenses, such as the case of current smokers earning less than $50,000 per year in this sample. This study highlights the need for intensive individualized tobacco treatment in breast cancer patients, utilizing effective and affordable modalities of counseling and medication.

The study is not free of limitations. Quitting date and use of cessation aid were not ascertained and thus it is unclear whether former smokers quit before or after breast cancer diagnosis and treatment. However, the available data were sufficient to achieve the overall goal of this study, which was to examine the characteristics of former smokers and compare them to breast cancer survivors who reported current smoking. A follow up study is warranted to uncover potential barriers to smoking cessation in order to individualize tobacco treatment to meet the needs of motivated light smoker cancer patients.

This pilot study revealed that, some women, albeit a small proportion, with a history of breast cancer treatment continue to smoke despite the health and financial benefits associated with smoking cessation. The findings also suggest that lower income is a risk factor for smoking among women with a history of breast cancer. Further investigation is important to shed light on potential barriers to successful cessation in breast cancer survivors and to identify ways to increase their cessation success rate.

Contributors

Steven Coughlin designed and implemented the parent study. Deepak Ayyala conducted the statistical analysis. Ban Majeed conceptualized the study and wrote the first draft of the manuscript. All authors contributed to and approved the final version of the manuscript.

Conflict of interest

The authors declare they have no conflicts of interest.

Ethics

This study was approved by the Augusta University Institutional Review Board and was compliant with ethical standards.

Informed consent

The informed consent of research participants was obtained.

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Thanks Letter to Peer Reviewers

All members of Current Cancer Reports (CCR) editorial office would like to extend greetings and sincere thanks to the peer reviewers. Thanks for their invaluable professional service to CCR. Without their help, it would not be possible for the journal to finish this full issue of existence with 8 high-quality articles published by 29 different authors.

For next issue, CCR will continue to make efforts to improve the quality and service level of manuscript submission. We look forward to their continuous cooperation with us to improve the quality of manuscripts and contribute to the development of CCR.

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